# A STUDY OF MEDICATION-TAKING FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER RECEIVING ORAL TARGETED THERAPY

by

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**A STUDY OF MEDICATION-TAKING FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER TAKING ORAL TARGETED THERAPY**

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors increase survival and improve quality of life for patients with non-small cell lung cancer (NSCLC). Because oral EGFR inhibitors are a new therapy, the implications for medication-taking are unknown. We used grounded theory to explore the process of medication-taking for patients with NSCLC who were receiving therapy with oral EGFR inhibitors. We sought to describe the medication-taking process and identify factors influencing medication-taking. We enrolled men and women from a National Cancer Institute-designated cancer center aged 18 years or older with NSCLC receiving oral EGFR inhibitors who were able to speak, read, and understand English. Exclusion criteria included central nervous system metastases and evidence of cognitive impairment as assessed by the Mini-Mental Status Exam. Thirteen participants were purposively selected for variation in gender (5 men/8 women), race/ethnicity (2 non-whites), age (52-83 years), time in therapy (one week to six or more years), dose reductions ($n$ = 5), and therapy discontinuation ($n$ = 2). Theoretical sampling focused on age and health insurance carrier. Data were collected through 32 semiformal and brief interviews concerning one's medication-taking behaviors related to therapy with oral EGFR inhibitors. We employed constant comparative and dimensional analyses. The basic psychosocial process, *Surviving Lung Cancer*, which participants framed within the recognition of NSCLC as a life-limiting illness without cure, included a dynamic process of (a) *Deciding* to take targeted therapy with erlotinib, (b) *Preparing* for erlotinib, and

(c) *Treating* lung cancer as a chronic condition. Participants described thresholds that may result in stopping erlotinib, including side effects and cost. Men described taking erlotinib therapy in partnership with their spouse; most women managed erlotinib alone. These findings may provide the theoretical basis for developing patient-centered interventions to address medication-taking.

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## PREFACE

One of the first things I learned when I entered the PhD program in 2007 was that it takes a village to conduct research. My village is huge, and I am eternally grateful to my mentors (and now friends), family, and friends for their direction and support throughout this journey. I am indebted to my dissertation committee for their guidance, patience, and care in teaching me to become a research scholar: Dr. Judith Erlen, my dissertation committee chair, for her guidance and support, for being a role model in all things academic and beyond, and her mentorship; Dr. Catherine Bender, my NRSA co-sponsor, for her oncology expertise, gracious support, and friendship; Dr. Mary Beth Happ, who taught me so many things, including the beauty of qualitative research and baseball; Dr. Sandra Engberg, my original academic advisor who has been on this journey with me from PhD entrance interview, to Switzerland, and back again; and, Dr. Ahmad Tarhini, for his guidance and for reminding me that I really do love clinical practice.

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men and women and their family and friends were extraordinary. Four did not survive to see the end of this project—I hope I have made them all proud.

# 1.0 INTRODUCTION

Traditionally, patients with non-small cell lung cancer (NSCLC) have been treated with surgery, radiation therapy, and/or intravenous (IV) chemotherapy. However, in recent years a paradigm shift has occurred in the approach to NSCLC treatment to the use of oral targeted therapies, such as tyrosine kinase inhibitors (Aisner, 2007). For patients with NSCLC clinical development of novel, oral targeted therapies has focused on the epidermal growth factor receptor (EGFR) with some agents already approved for clinical use. One such agent, erlotinib (Tarceva®, OSI Pharmaceuticals, Farmingdale, NY), an EGFR tyrosine kinase inhibitor, has been shown to increase survival, decrease tumor-related symptoms, and improve physical functioning and overall quality of life (QoL) in patients with NSCLC (Bezjak et al., 2006).

Adherence is only one aspect of medication-taking, a multifaceted process requiring one to perform complex activities such as identifying and counting pills, timing pill taking, and refilling medication prescriptions (Russell, Kilburn, Conn, & Ashbaugh, 2003). While assessment of adherence describes how closely an individual follows a prescribed regimen, assessment of medication-taking behavior illustrates how individuals take their medicines. Unfortunately, the process of medication-taking in patients with NSCLC taking oral targeted therapy has not been studied. Therefore, the purpose of this qualitative, grounded theory study was to explore the process of medication-taking for adult patients with NSCLC receiving oral

EGFR inhibitor therapies. Specifically, we aimed to (a) describe the process of medication-taking, and (b) identify factors influencing medication-taking regarding their prescribed regimen.

# 2.0 BACKGROUND

Understanding the process of medication-taking in relation to EGFR tyrosine kinase inhibitor therapy requires addressing the treatment of NSCLC and the challenges patients and health care providers face with regard to medication-taking. The following four sections provide (a) an overview of NSCLC, past and current treatments, and the benefits and challenges of oral targeted therapy; (b) a brief summary of the general state of the science concerning medication-taking and adherence for patients with chronic disorders; (c) a summary of what is known regarding medication-taking and adherence for patients with cancer who are taking oral cancer therapies; and (d) a summary of what is known regarding adherence and genetics for patients with cancer.

## 2.1 NON-SMALL CELL LUNG CANCER AND ORAL TARGETED THERAPY

Cancer is the second most common cause of death in the US exceeded only by heart disease (American Cancer Society [ACS], 2011). Lung cancer is the leading cause of cancer deaths in the US for both men and women with approximately 160,340 (87,750 men, 72,590 women) deaths estimated for 2012 (Siegel, Naishadham, & Jemal, 2012). In fact, lung cancer accounts for approximately 28% of all cancer deaths; more individuals die from lung cancer than from colon cancer, breast cancer, and prostate cancer combined (ACS, 2011). About 80% of new lung cancer cases are former or never smokers (The Centers for Disease Control and Prevention,

2007). The 5-year relative survival rate for persons of all stages is 16% (Siegel et al., 2012). Black males have higher lung cancer incidence and mortality rates than all other male racial groups as well as a lower 5-year relative survival rate (12%) (ACS, 2011). From 2004-2008, the average incidence of lung cancer among black men was higher than that of white men, but lower for black women than for white women (Siegel et al., 2012).

NSCLC adenocarcinoma is largely a disease of older adults (Edwards et al., 2002; Edwards et al., 2005; Horn, Visbal, & Leighl, 2007; Molina, Yang, Cassivi, Schild, & Adjei, 2008). The mean age at diagnosis is 71 years of age. Approximately two out of three individuals are older than 65 years of age at diagnosis and only 3% are younger than 45 years of age at diagnosis (ACS, 2011); therefore, lung cancer represents a major disease burden in older adults (Ganti, deShazo, Weir, & Hurria, 2012). Overall, approximately 70% of patients with NSCLC are diagnosed at an advanced stage (stage III/IV), are over 65 years of age at the time of diagnosis, and have a 16% five-year relative survival rate (Horn et al., 2007; Molina et al., 2008).

Lung cancer is typically diagnosed as one of two types: (a) small cell, constituting approximately 15-20% of lung cancer cases, is generally associated with smoking, and usually occurs in the bronchus or bronchi; and (b) NSCLC, comprising approximately 80-85% of lung cancer cases, occurs in both smokers and nonsmokers, is usually found in the periphery of the lungs (National Comprehensive Cancer Network [NCCN], 2011). NSCLC can be further classified into two main types: (a) nonsquamous which includes adenocarcinoma, large-cell, and other cell types; and (b) squamous including epidermoid. Bronchoalveolar carcinoma (BAC) is a less invasive type of NSCLC and is characterized by slow-growing well-differentiated cells (Neal, 2010). Adenocarcinoma can be further classified into three subtypes: bronchoid,

squamoid, and magnoid (Finkelstein, Ettinger, & Ruckdesschel, 1986). Approximately 55-65% of all lung cancers are NSCLC adenocarcinoma (Genentech, 2008).

Treatment of lung cancer is based on tumor histology and staging according to the TNM (primary tumor [T], evidence of regional nodes [N], and metastases [M]) guide (Lababede, Meziane, & Rice, 2011). Clinical effectiveness of NSCLC treatment is generally measured through effects on patient survival, QoL, and adverse effect profile (Horn et al., 2007). For earlier disease stages (Stages I and II) surgery provides the best chance for a cure (Bonomi, 2003; NCCN, 2011). For individuals with advanced disease stages (Stages IIIB/IV) surgical resection is not considered to be a viable option; rather, individuals may benefit from systemic treatment that prolongs survival and alleviates symptoms (Bonomi, 2003) such as IV chemotherapeutic regimens.

Chemotherapy with platinum-based agents is considered to be the standard of care as first line treatment in persons with good performance status (PS) (Eastern Cooperative Oncology Group [ECOG] PS 0, 1, or 2) (Horn et al., 2007; Maione et al., 2010). Paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan are IV chemotherapeutic agents that have been shown to have significant single-agent activity against NSCLC (Genentech, 2008). Common side effects of IV platinum-based or taxane chemotherapy include nausea, vomiting, diarrhea, fatigue, and peripheral neuropathy (Taxol® Package Insert, 2008). In addition, radiation therapy has been used since the 1950s as local therapy for NSCLC and is commonly used to treat painful bone metastases, although innovative techniques have been developed to improve clinical outcomes and decrease side effects (Davies, Houlihan, & Joyce, 2004).

Advances in treatment for NSCLC have included bevacizumab (Avastin®) (Genentech, Inc.; San Francisco, CA), a monoclonal antibody that inhibits the vascular endothelial growth

factor receptor. When added to platinum-based chemotherapy, bevacizumab has improved clinical outcomes. In a clinical trial of 878 patients with recurrent or advanced NSCLC (Stage IIIB/IV), patients treated with bevacizumab (every three weeks until disease progression) and chemotherapy (every three weeks for six cycles) had a median survival of 12.3 months, versus 10.3 months for those treated with chemotherapy alone (Maione et al., 2010; Sandler et al., 2006). Bevacizumab is now approved for first-line therapy for treatment with paclitaxel and carboplatin for patients with nonsquamous NSCLC. Most recently, a chemotherapeutic agent, pemetrexed (Alimta®) (Eli Lilly, Indianapolis, IN) has been approved as first-line therapy in combination with cisplatin and alone as maintenance therapy for patients with advanced nonsquamous NSCLC (Maione et al., 2010).

Positive prognostic indicators of NSCLC include early stage of disease at diagnosis, good PS (ECOG PS 0, 1, or 2), no significant weight loss (5%), and female gender (Hayes et al., 2006). Biological prognostic factors, such as mutation of the tumor supressor gene p53 or inactivation of the Kirsten-Rou sarcoma (K-ras) virus gene may be predictive of poor prognosis (Horio et al., 1993; Massarelli et al., 2007; Slebos et al., 1990). Even in cases with positive prognostic indicators, late diagnosis represents a primary barrier to improving NSCLC outcomes.

Chemotherapy and radiation therapy have modest response rates with respect to QoL and overall survival; however, the efficacies of traditional treatments have plateaued (Bunn & Thatcher, 2008) and most patients succumb to the disease within two years (Gridelli et al., 2007). Chemotherapy and radiation therapy are complicated and expensive, are nonselective in that they affect dividing cells in the body, and have significant adverse effect profiles that may undermine overall treatment goals by exchanging disease symptoms for treatment related adverse effects (Gridelli et al., 2007). Additionally, NSCLC treatment is costly; annual direct medical care costs

of lung cancer in the US were estimated to be approximately US $10.3 billion in 2006 (National Cancer Institute [NCI], 2011) (current estimates not available), which represents approximately one-tenth of direct medical care expenditures for cancer treatment (Horn et al., 2007). Costs may be significantly higher for patients who receive than for those who do not receive chemotherapy. Therefore, researchers and clinicians have identified a significant need for more novel treatment approaches selectively pinpointing specific receptors in cancer cells (Bunn & Thatcher, 2008).

### 2.1.1 Oral targeted therapy

Targeted therapies act on, or "target", specific sites on or in cancer cells in order to stop or slow tumor growth (NCI, 2008). The first targeted therapies were IV monoclonal antibodies, with the first of these approved in 1997 for the treatment of non-Hodgkin's lymphoma. Oral, small molecule, targeted therapies comprise about 5% of currently available anticancer therapies; however, they represent 25% of all cancer therapies in development (Bedell, 2003). Most recently, targeted therapies under development and approved for use for patients with NSCLC include oral EGFR inhibitors and therapies targeting the rearrangement of echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) (Table 1).

**Table 1: Tyrosine kinase inhibitors approved for patients with cancer**

| Generic name | Trade Name | Year Approved | Manufacturer | Target Gene or Receptor | Disease Process |
|---|---|---|---|---|---|
| Dasatinib | Sprycell® | 2006 | Bristol-Myers Squibb | BCR-ABL | Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) |
| Imatinib | Gleevec® | 2001 | Novartis | BCR-ABL | Ph+ CML<br>Gastrointestinal stromal tumors (GIST) |
| Nilotinib | Tasigna® | 2007 | Novartis | BCR-ABL | Ph+ CML |
| Gefinitib | Iressa® | 2003 | AstraZeneca | EGFR | Non-small cell |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | lung cancer (NSCLC) |
| Erlotinib | Tarceva® | 2004 | OSI Pharmaceuticals | EGFR | NSCLC<br>Pancreatic cancer |
| Crizotinib | Xalkori® | 2011 | Pfizer | EML4-ALK | NSCLC |
| Lapatinib | Tykerb® | 2007 | GlaxoSmithKline | EGFR, HER2/neu | Breast cancer |
| Sunitinib | Sutent® | 2006 | Pfizer | PDGFR, VEGF, KIT, RET, CSF-1R, flt3 | GIST<br>Renal cell carcinoma (RCC) |
| Sorafenib | Nexavar® | 2006 | Bayer | VEGF, PDGF, C-Raf, B-Raf, MAP Kinase, c-kit | RCC<br>Hepatocellular carcinoma |
| Pazopanib | Votrient™ | 2009 | GlaxoSmithKline | VEGF, c-kit, PDGFR | RCC<br>Soft tissue sarcoma |

Note. BCR-ABL = fusion of Abelson (Abl) tyrosine kinase gene at chromosome 9 and break point cluster (Bcr) gene at chromosome 22; EGFR = epidermal growth factor receptor; EML4-ALK = rearrangement of echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; HER2/neu = one of four membrane proteins in EGFR family; PDGFR = platelet-derived growth factor receptor; VEGF = vascular endothelial growth factor; RET = proto-oncogene, encodes receptor tyrosine kinase for the neurotrophic factor family; CSF-1R = colony stimulating factor 1; flt3 = encodes receptor tyrosine kinase that regulates hematopoiesis; MAP Kinase = family of serine/threonine proteins responsible for regulating cellular activities, such as apoptosis; c-kit = tyrosine kinase stem cell factor receptor.
Source: National Cancer Institute (www.cancer.gov).

### 2.1.2 Epidermal growth factor receptor (EGFR)

EGFR is a family of four membrane proteins that are structurally similar to tyrosine kinase proteins: ErbB1 (EGFR; Human Epidermal Growth Factor Receptor Type 1 [HER1]), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4) (Jones, 2003). Activation of EGFR results in tumor growth stimulation and progression (Molina et al., 2008). EGFR is over-expressed in most squamous subtypes and in 80-85% of non-small cell lung cancers (Harari, 2004; NCCN, 2011; Press & Lenz, 2007). Thus, these new oral agents such as erlotinib (Tarceva®, OSI Pharmaceuticals, Farmingdale, NY) and gefitinib (Iressa®, AstraZeneca, Wilmington, DE) were developed to inhibit EGFR over-expression. Gefitinib was approved for use in 2003 for salvage treatment of advanced NSCLC; however, it was withdrawn from the market in June 2005 due to

the incidence of interstitial lung disease (Gridelli et al., 2007). The FDA has restricted its use to individuals in a clinical trial or those benefiting from treatment (Harari, 2004).

Erlotinib blocks the activity of HER1/EGFR, and was approved for use in 2004 for 2nd and 3rd line treatment of advanced NSCLC. In a randomized clinical trial, erlotinib was the first oral EGFR inhibitor to show an increase in median overall survival (6.7 months compared to 4.7 months for placebo, $p = 0.001$) and progression free survival (2.23 months versus 1.84 months for placebo, $p = 0.001$) (Tarceva® Package Insert, 2010). In April 2010, erlotinib was approved for maintenance therapy for patients with advanced stage NSCLC who had stable disease (cancer had not grown or spread) after initial treatment (4 cycles) of chemotherapy. In addition, research has shown that approximately 10% of patients with NSCLC have EGFR mutations (Fukuoka et al., 2003; Kris et al., 2003), specifically deletions of exon 19 (45%) and exon 21 (40%), and respond well to EGFR inhibitor therapy (Miller et al., 2008; Sequist et al. 2008). As such, the NCCN (2011) recommends treatment with erlotinib as first-line therapy for those patients with NSCLC with EGFR mutation. Generally, patients remain on therapy with erlotinib until evidence of disease progression or they experience unacceptable toxicity (Tarceva® Package Insert, 2010).

### 2.1.3 The advantages and disadvantages of oral targeted therapy

Cutting edge agents, such as oral EGFR inhibitors, are clearly beneficial; however, they present new challenges when prescribed for individuals with NSCLC. First, since persons with advanced cancer are living longer, they may be taking anticancer or other supportive therapies on a continual basis for up to 20 years (Szetela & Gibson, 2007). Therefore, the expense of long-term oral targeted therapy may result in a substantial burden to persons with NSCLC and their families. For example, it is estimated that a 30-day supply of 150 mg erlotinib tablets may cost

US $2,330 (Securities Exchanges Commission, 2008). Furthermore, Medicare reimbursement is problematic; oral cancer agents are covered under Medicare parts B and D, but require selection of a prescription medication plan and monthly premiums (Bartel, 2007; Winkeljohn, 2007). Medicare Part B covers 80% of the costs of IV chemotherapy or their oral equivalent (Conwell et al., 2011). Medicare Part D covers the cost of most oral targeted therapies; however, patients with high medication costs (such as NSCLC) have difficulty with the "doughnut hole", where patients are responsible for all costs in the spending thresholds between $2,510-$5,726 (Bach, 2009; Conwell et al., 2011).

Further complicating oral targeted therapy use is the timing of dosing regimens and unique side effect profiles. Patients undergoing therapy with erlotinib are instructed to take their dose either one hour before or two hours after a meal since food considerably changes its bioavailability and may increase the risk of adverse events (Tarceva® Package Insert, 2010). Generally, oral targeted therapies are considered to be less toxic than IV chemotherapy but have distinctive side effect profiles due to pathway-specific mechanisms of action. By far, the most common side effect of erlotinib is a generally mild to moderate, dose-dependent papulopustular rash (PPR) that affects the face, neck, and upper trunk (Perez-Soler et al., 2005; Viele, 2007). PPR occurs in 45% to 100% of patients (Perez-Soler & Saltz, 2005; Perez-Soler et al., 2005; Segaert & Van Cutsem, 2005). The exact role of HER1/EGFR in skin is not well understood, though the sebaceous glands are usually not affected (Perez-Soler & Saltz, 2005). Testing with immunohistochemistry and in situ hybridization has shown upregulation of the negative epidermal-growth regulator $p27^{Kip1}$ (Busam et al., 2011). In fact, $p27^{Kip1}$ increased 3 to 4 times by the eighth day of treatment with cetuximab, an intravenous EGFR inhibitor (Busam et al., 2011).

Skin toxicity has been suggested as a proxy marker for clinical effectiveness of oral EGFR inhibitors (Eames et al., 2010); however, an explanation for the relationship between the rash and response to EGFR inhibitor therapy is elusive (Amador et al., 2004). One reason could be the potential for genetic differences among individuals. Amador and colleagues (2004) found a correlation between CA-single sequence repeats (CA-SSRs) in patients with head and neck squamous carcinoma and increased response to oral EGFR inhibitor therapy. Specifically, individuals with shorter CA dinucleotide repeats had higher incidence of rash when treated with oral EGFR inhibitors.

Other dermatological toxicities such as trichomegaly, conjunctivitis and dry eye, hair changes, fatigue, and interstitial lung disease have been reported with erlotinib use (Lynch et al., 2004). In addition, EGFR-inhibition associated diarrhea is experienced by approximately 75% of patients taking erlotinib (Sipples, 2006).

No randomized clinical trials of agents for treating EGFR inhibitor-associated rash have been conducted and no established guidelines exist (Perez-Soler et al., 2005), although algorithms have been developed at the institution level. Rash related to EGFR inhibitor therapy is commonly treated with thick, emollient moisturizers, topical corticosteroids, topical antibiotics, and/or dose reductions (NCI, 2008). Erlotinib-related diarrhea is generally treated with loperamide or diphenoxylate and atropine. Depending on the grade and severity of side effects, targeted therapy doses may be reduced or delayed (Bartel, 2007); for example, if untreated, dermatological toxicities can result in reduction in EGFR dose for 72% of episodes or discontinuation in 30% of episodes (Boone et al., 2005). Dermatological toxicities of oral EGFR inhibitors can affect patients' health-related quality of life (Joshi et al., 2010), but the

implications of dose reductions and dose delays on disease progression and overall survival are not yet known.

Despite these challenges, oral targeted therapy clearly has its advantages over traditional cancer therapies. The most advantageous aspects of oral targeted therapy are the flexibility and independence these therapies offer (Jones, 2003). Oral targeted therapies provide more prolonged drug exposure and may reduce the use of health care resources (Aisner, 2007); for example, office visits may be reduced, and therefore patients may spend less in terms of required office visit co-pays (Bartel, 2007). Additionally, EGFR inhibitors, whether administered alone or in combination with chemotherapy, may lead to improved clinical outcomes (Abou-Jawade, Choueiri, Alemany, & Mekhail, 2003), such as improved survival and reduced symptoms. Future directions for clinical research include combining targeted therapy with IV chemotherapy or other targeted therapies, such as bevacizumab; development of new targeted therapies, such as crizotinib (Xalkori®, Pfizer, New York, NY) which targets EML4-ALK; and, examining the effects of targeted therapy in patients with previously treated brain metastases (Sandler, 2008). However, these increasingly complex regimens may further compound the side effects of oral targeted therapy. Oral targeted therapies may be examined alone or with another therapy in a clinical trial, which may potentially decrease costs for a patient; however, not all oral targeted therapies are provided free of cost in clinical trials. Additionally, costs of the agents and lack of Medicare reimbursement may result in an increased financial burden for patients and their families. Finally, treatment costs may increase as survival rates rise and therapies are taken for longer periods of time.

### 2.1.4 Summary

Oral EGFR inhibitors provide patients with an efficacious, less invasive, and more convenient treatment for NSCLC, potentially resulting in an increase in QoL as compared to IV chemotherapy and a sense of control over treatment (Bartel, 2007), but the costs, unique side effect profiles, and changing dose regimens bring increased challenges for health care professionals in monitoring and assessing medication-taking behavior. Although some information is available regarding the association between IV chemotherapy adherence and disease-free survival, there is no evidence specifically related to oral EGFR inhibitors adherence and overall patient survival. Moreover, prior research demonstrates that patients have difficulty adhering to daily administration of oral targeted therapies, highlighting the imperative of monitoring patient adherence (Jones, 2003). Because there is little evidence of research evaluating medication-taking or adherence in patients with NSCLC receiving oral EGFR inhibitors therapy, a qualitative study exploring the process of medication-taking of oral targeted therapy in patients with NSCLC was a critical first step in a program of research to improve clinical outcomes for these patients.

## 2.2 MEDICATION-TAKING AND ADHERENCE FOR PATIENTS WITH CHRONIC DISORDERS EXCLUDING CANCER

The terms “adherence” and “medication-taking” are often used interchangeably in the literature, but there is a distinction between the two concepts. Medication-taking is a process that requires one to perform activities including identifying pills, counting pills, timing pill taking, and

refilling medication prescriptions (Russell et al., 2003). Medication-taking represents the work of adherence (McCoy, 2009), the "extent to which patients follow the instructions they are given for prescribed treatment" (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008, p. 2). Estimates are that 50% of patients with chronic disorders are nonadherent to their prescribed drug regimens (Dunbar-Jacob et al., 2000). The costs to the US health care system of nonadherence in patients with chronic diseases are estimated to be US $300 billion a year (DiMatteo, 2004). Furthermore, nonadherence to prescription medication has been linked to increased emergency room visits, increased psychiatric admissions, increased nursing home admissions, and poor health status (Piette, Heisler, & Wagner, 2004).

### 2.2.1 Medication-taking

Assessment of medication-taking behavior illustrates how individuals actually take their medicines. Qualitative inquiry has provided essential and unique information concerning the medication-taking experiences for patients with chronic disorders excluding cancer, which is summarized in Table 2.

**Table 2: Qualitative studies of medication-taking in patients with chronic conditions excluding cancer**

| Authors | Sample size (*N*) | Method | Chronic condition | Sampling method | Analytic approach | Results |
|---|---|---|---|---|---|---|
| Bacjar, 2006 | 10 | Grounded theory | General chronic condition | Maximum variation; theoretical | Constant comparative analysis | Model of medication-taking practice: making sense of medication-taking, medication-taking acts, medication-taking self-assessment. |
| Chambers et al., 2011 (adherence) | 26 | Qualitative descriptive comparison of high- and low-adherers | Stroke | Purposive | Thematic analysis | Major themes: importance of stability of a medication routine and beliefs about medication. |
| Chen et al., 2007 | 19 | Grounded theory | Cardiovascular disease | Purposive; theoretical | Constant comparative analysis | Behavioral model for elderly patients with chronic diseases comprised of four themes: perceived effectiveness, perceived partnership, perceived reality, and interpersonal influences. |
| Clatworthy et al., 2007 (adherence) | 16 | Qualitative description | Bipolar disorder | Convenience | Coding structured around Self-Regulation Model and Necessity-Concerns Framework | Concepts concerning intentional and unintentional adherence. |
| Dowell & Hudson, 1997 | 50 | Grounded theory | General practice | Convenience | Iterative | Eight decision-making themes with 39 sub-categories. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Gray, 2006 (adherence) | 11 | Grounded theory approach | HIV/AIDS | Purposive; | Analytic coding | Five themes: choosing life, riding it out, figuring it out, sticking to it, realizing the benefits. |
| Erlen & Mellors, 1999 (adherence) | 6 | Qualitative description | HIV/AIDS | Purposive | Thematic analysis | Four major themes: decision-making regarding initiating treatment, difficulties, problem solving, and quality of life. |
| Hon, 2012 (adherence) | 12 | Grounded theory approach | Adults receiving antipsychotic medication (bipolar, schizophrenia, schizo-affective disorder) | Purposive until theoretical saturation | Constant comparative analysis | Quality of life, health status, and discernment that were inter-related with a cyclical outcome. Core category was quality of life. |
| Johnson et al., 1999 | 21 | Qualitative description | Older adults (< 65 years) with hypertension | Convenience | Constant comparative content analysis using the ethnograph program for data management | Four major domains: purposeful adherence, patterned adherence, purposeful nonadherence, and unintentional nonadherence. |
| Lehane et al., 2008 | 10 | Qualitative description | Coronary artery disease | Convenience | Content analysis | Three themes: keeping track, reasoning about medications, social/ professional influences. |
| Lewis et al., 2006 (adherence) | 13 | Qualitative description | HIV/AIDS | Purposive (100% adherent to therapy) | Content analysis | Core category: successful medication management.<br><br>Three sub- |

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|---|---|---|---|---|---|---|
| | | | | | | categories: regimen, self, and environment. |
| McCoy, 2009 (adherence) | 79 | Sub-study of larger study, institutional ethnographic approach | HIV/AIDS | Purposive | Institutional ethnographic approach | Realizing the medication day: scheduling, realizing dose time, keeping track, and managing the problem of will. |
| Orr et al., 2007 (adherence) | 26 | Phenomenology | Adult renal transplant | Purposive | Thematic analysis (Krueger, 1998); constant comparison (Strauss &Corbin, 1990). | Themes: fear of transplant failure, loyalty to the renal team and donors, health beliefs, forgetting and side effects. |
| Proulx et al., 2007 (non-compliance) | 27 | Qualitative description | High blood pressure | Purposive | Content analysis | Broad categories: stress and living conditions in the occasional skipping or deferral of medication-taking; doubt as the motivating factor for transitory, irregular medication use; subjective risk as the motivating factor for persistent irregular use. |
| Reid et al., 2006 | 17 | Qualitative description | Congestive heart failure | Purposive | Constant comparative | Knowledge of their condition, complexity of medication taken, strategies, low concordance, teaching and learning. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Remien et al., 2003 (adherence) | 110 | Qualitative description | HIV/AIDS | Convenience | Grounded theory principles | Prevalent themes: ambivalence towards HIV medication, intentional nonadherence related to side effects. |
| Rifkin et al., 2010 (adherence) | 20 | Qualitative description | Chronic kidney disease | Convenience (<55 years of age) | Qualitative data analysis (not specified) | Four themes: concerns about polypharmacy, medication prioritization, experiences with side effects, and barriers to discussions of adherence with physicians. |
| Ruppar & Russell, 2009 (adherence) | 19 | Qualitative description | Kidney transplant recipients | Convenience | Constant comparative analysis | Four themes: reminder methods, obtaining medications, maintaining routines, and problem-solving strategies. |
| Russell et al., 2003 | 16 | Qualitative description | Adult renal transplant | Purposive | Manifest content analysis, guided by Theory of Planned Behavior. Comparisons between those > and <50 years of age. | Four categories: behavioral, normative, control, and problem-solving. |

Note. HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome. Studies that examined the work of adherence but used the term "adherence" or "non-compliance" to represent medication-taking are denoted with (adherence) or (non-compliance).

### 2.2.2 Adherence

For individuals with chronic disorders, more research has focused on adherence, the outcome of medication-taking. Factors associated with adherence have been studied in numerous patient

samples undergoing therapies with varying regimen complexity (Osterberg & Blaschke, 2005; World Health Organization [WHO], 2003). These factors include the patient-provider relationship, patient beliefs, complexity of dosing regimen, side effects, and other cognitive factors such as forgetting (WHO, 2003). For example, Choo and colleagues (1999) reported that baseline items regarding forgetting to take medication were significantly predictive of adherence to antihypertensive medication and also correlated with concurrent pharmacy refilling records. Similar findings have been uncovered in other populations, including patients prescribed complex treatment regimens, for example, patients with renal transplantation (Butler et al., 2004) and women with HIV taking protease inhibitors (Erlen, Sereika, Cook, & Hunt, 2002).

Accurate measurement of adherence is a challenge in adherence research. First, there is no agreement on what defines adequate adherence (Osterberg & Blaschke, 2005). The most widely accepted rate for patients with chronic conditions is 80%; higher rates of 95% have been proposed for persons with serious conditions, such as HIV infection (Osterberg & Blaschke, 2005), as higher rates of adherence are needed for optimal viral suppression (Rosenblum, Deeks, van der Laan, & Bangsberg, 2009). For studies of medication adherence for patients with cancer taking oral cancer therapies, the accepted rate for patients with chronic illnesses (80%) is most often implemented. Second, there are varying measurement methods of adherence. Electronic monitoring has been considered the “gold” standard (DeGeest et al., 2006; Evangelista et al., 2003) since it can detect lower levels of adherence. Direct methods of adherence assessment, such as continuous dose observation and evaluation of pharmacologic blood levels, provide accurate data but are inconvenient, invasive, costly, and difficult to implement in everyday practice (Macintosh, Pond, Pond, Leung, & Siu, 2007; Osterberg & Blaschke, 2005). Indirect methods, such as pill counts and patient self-report, are inexpensive and convenient for clinical

practice (Rolley et al., 2008); however, these methods tend to overestimate adherence due to challenges with patient recall or social desirability (Osterberg & Blaschke, 2005), and pill counts verify that one took the right number of pills, but not whether they were taken on schedule (Macintosh et al., 2007).

### 2.2.3 Summary

Prior medication-taking and adherence research examining patients with chronic illnesses, such as hypertension, renal transplantation, and HIV/AIDS, has demonstrated that there are many factors associated with medication-taking and adherence, as well as measurement challenges of adherence. Knowledge gained from research in these patient samples can inform medication-taking research in patients with cancer; however, oral EGFR inhibitors therapy presents specific challenges concerning dosing, cost, and management of side effects. The unique factors that influence the process of medication-taking for patients with NSCLC taking these therapies remain unknown. Therefore, a qualitative study exploring the process of medication-taking in patients with NSCLC receiving oral targeted therapy was an appropriate, critical first step.

## 2.3 MEDICATION-TAKING AND ADHERENCE FOR PATIENTS WITH CANCER

### 2.3.1 Medication-Taking

Little research has focused on the medication-taking experiences for patients with cancer. Kingsnorth and Wilkinson (1996) examined nonadherence to palliative care medications for

patients with cancer; intentional nonadherence due to lack of understanding about the medication and challenges such as forgetting, difficulty taking, or lack of access to the medication comprised the major themes. Ersek, Kraybill, and Du Pen (1999) explored the reasons patients with cancer have trouble taking their pain medication; however, the purposes of analgesia and palliative care medications are different from that of medications for active treatment of NSCLC.

One published report of a qualitative descriptive study that assessed adherence to capecitabine (oral chemotherapy) for patients with breast cancer and colon cancer was found (Denois et al., 2011). Forty-two patients and 10 oncologists from two clinics in France participated in either individual or group interviews to discuss their experiences with capecitabine. Use of oral chemotherapy was noted to be a major change for oncologists, who had varying attitudes toward prescribing capecitabine. Most of the oncologists did not specifically ask their patients about adherence to capecitabine. The major themes expressed by the patients concerned their adherence with dose and schedule, information, communication, and evaluation of side effects. While the results of this study provided information about patients' observance of dosing schedule and inability to identify and report toxicities, it should be noted that capecitabine is an oral chemotherapeutic agent that is generally prescribed alone or in combination with another therapy for a finite period of time. EGFR tyrosine kinase inhibitor therapy for treatment of NSCLC has a different mechanism of action, different side effect profiles, and is generally taken until disease progression (weeks to years).

### 2.3.2 Adherence

Adherence to oral cancer therapy has been identified as a significant problem by clinicians and has been evaluated in patients with lymphoma, acute lymphocytic leukemia (ALL), breast

cancer, gastrointestinal stromal tumors (GIST), ovarian cancer, and non-Hodgkin's lymphoma (Mazzeo et al., 2011; Waterhouse, Caizone, Mele, & Brenner, 1993) with adherence rates ranging from less than 20% to 100% (Partridge, Wang, Winer, & Avorn, 2003). No published studies were identified addressing medication-taking or adherence for patients with NSCLC. Most data regarding adherence to oral cancer therapy, including medication-taking beliefs and factors associated with adherence, are based on studies of women with breast cancer taking oral hormonal therapy with either tamoxifen (Viele, 2007) or anastrozole (Partridge et al., 2008) or patients with leukemia taking oral targeted therapy with imatinib (Gleevec®, Novartis Pharmaceuticals Corporation, East Hanover, NJ) (Ganesan, et al., 2011; Ibrahim et al., 2011; Noens et al., 2009).

#### 2.3.2.1 Oral hormonal therapy for breast cancer

Generally, studies of tamoxifen report adherence rates to be 80% or less, but these rates are influenced by differences in measurement methods (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004; Lash, Fox, Westrup, Fink, & Silliman, 2006; Partridge et al., 2003; Waterhouse et al., 1993). Adherence to tamoxifen has been shown to relate to patients' awareness of risks associated with breast cancer, beliefs regarding the benefits of therapy, and the character and severity of side effects (Barron et al., 2007; Fink et al., 2004; Grunfeld, Hunter, Sikka, & Mittal, 2005; Lash et al., 2006; Love, Cameron, Connell, & Leventhal, 1991). For example, sociodemographic factors related to adherence to therapy with tamoxifen have been examined in a number of studies, but with mixed results. Kahn and colleagues (2007) evaluated patient-centered measures related to ongoing use of tamoxifen. Younger age (< 65) ($p$ = .04) was associated with ongoing tamoxifen use four years after diagnosis; however, no other demographic, clinical, cancer- or treatment-related factors were associated with ongoing

tamoxifen use. Partridge and colleagues (2003) found that both younger (< 45 years) and older women (> 65 to 85 years) were more likely to discontinue tamoxifen therapy than women ages 45 to 65. Fink and colleagues (2004) found that age was not associated with discontinuation of tamoxifen. Most recently, Sedjo and Devine (2011) reported that 23% of women were nonadherent at one year to their aromatase inhibitor therapy. The researchers reported that risk factors for nonadherence included younger age.

Fewer studies have found a relationship between race or ethnicity and adherence for women taking tamoxifen therapy. Partridge and colleagues (2003) found that non-white women were more likely to discontinue tamoxifen therapy than white women. Lebovits and colleagues (1990) found that women who discontinued oral chemotherapy had a significantly lower socio-economic status ($p < .02$) than women who continued their therapy; however, oral chemotherapeutic agents typically have a different side effect profile than that of oral hormonal therapies due to different mechanisms of action.

Women with higher breast cancer stage (Stage II) (Lebovits et al., 1990) and who had received chemotherapy before beginning tamoxifen (Fink et al., 2004) have been reported to be less likely to discontinue tamoxifen therapy. Kahn and colleagues (2007) reported that positive hormone receptor status was associated with ongoing tamoxifen use at four years; however, Fink and colleagues (2004) found that positive estrogen receptor status and positive nodes were associated with stopping therapy with tamoxifen by the second year. Partridge and colleagues (2003) found that women who had a mastectomy versus breast conserving surgery were more likely to be nonadherent to tamoxifen therapy.

The relationship between side effect severity and discontinuation of tamoxifen is unclear. Fink and colleagues (2004) reported that side effects were not associated with discontinuation of

tamoxifen, but other researchers have reported that women with side effects were more likely to stop taking tamoxifen (Demissie et al., 2001; Kahn et al., 2007). Grunfeld and colleagues (2005) reported that of the women who discontinued tamoxifen, 46% discontinued due to side effects.

Adherence rates to another hormonal agent for breast cancer, anastrozole, are similar to those reported for tamoxifen therapy. In a recent study defining adherence as a medication possession ratio (the number of days one had anastrozole or another oral endocrine therapy available) of 80% or greater, 72% to 81% of eligible women in three large datasets were considered to be adherent during their first year of anastrozole therapy (Partridge et al., 2008). Adherence declined to 62% to 79% at year three. Furthermore, a comparison of adherence to hormonal therapy for postmenopausal women with breast cancer demonstrated 80% adherence for women taking tamoxifen and 69% for women taking anastrozole (Ziller et al., 2009).

Nonadherence or nonpersistence to aromatase inhibitors related to side effects has been evaluated mostly in the context of clinical trials. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial (2002), there were fewer women who withdrew from therapy with anastrozole compared to tamoxifen; however, higher nonpersistence rates with aromatase inhibitors were noted in similar trials comparing exemestane and letrozole with tamoxifen (Coombes, Hall, & Gibson, 2004; Goss, Ingle, & Martino, 2003). In a qualitative analysis of the medication-taking experiences for women taking oral anastrozole therapy (Wickersham, Happ, & Bender, under review; Wickersham, Happ, & Bender, 2011; Wickersham, Happ, & Bender, 2010), despite side effect severity, most women (11/12) (91.7%) continued to take anastrozole due to a strong belief in its importance.

Few studies have compared rates of or factors affecting adherence to therapy with tamoxifen and anastrozole. Ziller and colleagues (2009) measured adherence in 100

postmenopausal women ($n$ = 50 tamoxifen, $n$ = 50 anastrozole) and found no correlation of adherence to any baseline characteristics or side effects. Atkins and Fallowfield (2006) found that younger women were more likely to non-adhere to oral treatment for breast cancer ($p$ = .015); disliking aspects of treatment was predictive of nonadherence. It should be noted that the sample of women included those taking oral chemotherapy, as well as women taking oral hormonal therapy. Side effects and reasons for discontinuation were not reported.

#### 2.3.2.2 Oral targeted therapy for chronic myeloid leukemia (CML)

Imatinib mesylate (imatinib) is a tyrosine kinase inhibitor that blocks the adenosine triphosphaste (ATP)-binding site of the BCR-ABL tyrosine kinase and has been shown to be effective in treating the chronic and accelerated phases of CML as well as blast crisis. Imatinib is generally prescribed at a starting dose of 400 mg/day. Individuals taking imatinib have received therapeutic benefit from 18 months to 7 years (Druker et al., 2001; Hehlman et al., 2005; Kantarjian et al., 2002; Schindler et al., 2000; Talpaz et al., 2009).

In the last five years, several published reports of research examining adherence to imatinib have become available. Darkow and colleagues (2007) found that the mean adherence rate in 267 persons with CML was 77% (measured by MPR); 30.7% failed to refill their imatinib prescription within 30 days. Adherence was lower in female patients, those with more concomitant medications, higher cancer complexity, and those taking higher doses of imatinib (600 mg/day or higher). Similar results were reported by Halpern, Barghout, Mody-Patel, & Williams (2008). Both Darkow and colleagues (2007) and Halpern and colleagues (2008) found that lower imatinib adherence was associated with higher medical expenditures.

The ADAGIO Study (Adherence Assessment with Glivec: Indicators and Outcomes) ($N$ = 169) examined the prevalence of nonadherence for patients with CML, the association of

determinants of adherence with measures of nonadherence, and whether treatment response is associated with adherence beliefs (Noens et al., 2009). Adherence was measured using the Basel Assessment of Adherence Scale (BAAS) with Immunosuppressive Medication, adapted for imatinib, and pill counts. The BAAS is a four-question interview guide; a positive answer to any of the four questions equals nonadherence. Only 14.2% of the participants had perfect 100% adherence. There were no significant associations between adherence behavior and length of illness or duration of treatment at baseline or follow-up. They found a weak correlation between the bothersomeness of symptoms and adherence per the BAAS ($r_{bs}$ = -240, $p$ = .007), but no other statistically significant correlations between BAAS and other variables. A multivariate analysis demonstrated that the patient-related variables associated with nonadherence were higher age, longer time since CML diagnosis, living along, male sex, longer time on imatinib therapy, higher doses of imatinib (600 mg or greater), higher degrees of chronic care, higher self-reported functional status, and quality of life. Participants with suboptimal response to imatinib had higher mean percentages of nonadherence (23.2%) than those with optimal responses (7.3%). Conversely, in a retrospective analysis of 430 persons with CML under the age of 65, key factors that were associated with nonadherence were lower age, shorter exposure to imatinib, lower starting dose (< 400 mg), longer lag time between CML diagnosis and filling of imatinib prescription, increased number of concomitant medications, and increased copayment (St. Charles et al., 2009).

Ganesan and colleagues (2011) retrospectively examined nonadherence in persons with chronic phase (CP) CML ($N$ = 516) in India. All participants received imatinib through the Glivec International Patient Assistance Program (GIPAP), because patients could not afford the drug as the marketed price. Five-year event free survival (EFS) and nonadherence rates were

estimated from the GIPAP database. Approximately one-third (29.6%) of the participants were nonadherent (interruption in therapy of more than 1 week). Univariate analysis demonstrated that prolonged symptom duration before diagnosis, treatment with hydroxyurea for more than one month prior to imatinib therapy, and nonadherence were associated with EFS. Only nonadherence was significant in the multivariate analysis (HR 1.6; $p = 0.048$). This study is significantly limited by the method of adherence measurement. Because one had to return to the clinic to obtain his/her bottle of imatinib, adherence was measured by identifying those who did not return to the clinic and subsequently had an interruption in more than one week in therapy. This method is convenient and takes advantage of existing adherence data, but it does not distinguish between those who attended clinic visits from those who were fully adherent.

Several studies have examined adherence to imatinib and response to treatment. Marin and colleagues (2010) found a strong correlation between adherence measured by a medication event monitoring system (MEMS) ($\leq$ 90% or > 90%) and the 6-year probability of a major molecular response (MMR) ($p = .001$) and a complete molecular response (CMP) ($p = .002$). Multivariate analyses showed that adherence and presence of molecular human organic cation transporter-1 (RR, 1.79, $p = .038$) were the only independent predictors of MMR. Adherence was the only independent predictor of CMR. Ibrahim and colleagues (2011) examined the association between MEMS adherence and the loss of a complete cytogenetic response (CCyR) and imatinib failure for patients with CML receiving imatinib ($N = 87$). The median adherence was 97.6%; 26.4% had adherence lass than or equal to 90%. Multivariate analyses showed that adherence rate and failure to achieve a molecular response were the only predictors for loss of CCyR and discontinuation of imatinib therapy.

#### 2.3.2.3 Oral chemotherapy for small cell lung cancer

One study of medication adherence in patients with small cell lung cancer was found. Lee and colleagues (1993) examined medication adherence in a sample of 12 patients receiving palliative treatment with low dose etoposide for relapsed small cell lung cancer by using an "intelligent tablet bottle" with reported 93% adherence. Medication-taking behavior and factors affecting adherence were not assessed.

### 2.3.3 Barriers to and interventions for adherence for patients with cancer

Potential barriers to medication-taking and suggestions for managing patient adherence have been identified for oral chemotherapeutic agents, such as capecitabine (Macintosh et al., 2007). Barriers include a patient's ability to identify his or her own medications, the ability to specify the correct dose and time of administration with respect to meals and other over the counter medications and cost (Aisner, 2007; Viele, 2007). In addition, individuals aged 70 years and older face unique challenges that may influence medication-taking behaviors related to oral targeted therapy, such as negotiating the effects of multiple co-morbidities (Jorgensen, Johansson, Kennerfalk, Wallander, & Svardsudd, 2001; Linjakumpa et al., 2002; Veehof et al., 2000), managing complicated medication regimens (Elliott, 2006) suffering from functional and cognitive declines and experiencing depressive symptomatology (Gray, Mahoney, & Bough, 2001; Spiers & Kutzik, 1995; Vik et al., 2006). The impact of these challenges on medication-taking for older adults with NSCLC remains unexplored.

Suggestions for adherence management for patients with cancer have included the use of blister packs and pill organizers, patient diaries, counseling regarding the unique adverse effects of specific oral agents, random pill counts, and follow up at clinic visits or by telephone using

questions specific to the promotion of patient monitoring and adherence (Macintosh et al., 2007; Szetela & Gibson, 2007; Viele, 2007; Winkeljohn, 2007). Little research has focused on the testing of these interventions in patients with cancer. Decker and colleagues (2009) developed a nursing intervention to monitor adherence using a Symptom Management Toolkit®, based on a modified health belief model approach, and an automated voice response (AVR) reminder system (once weekly for 10 weeks). Adherence was measured using a combination of medical record audit, patient report (name of oral agent, number of pills to be taken and when, number of days or weeks on/off per month or cycle), and pharmacy report. The intervention was tested in patients with breast, colon, and lung cancers receiving non-hormonal agents for treatment of their cancer. Adherence was defined as 100% (i.e., anything less was considered to be nonadherent). Findings showed a nonadherence rate of 23.3% due to symptoms and forgetting to take medication. An association between symptom management and adherence was reported; symptom severity and beliefs about medications were not significantly different between adherent and nonadherent patients.

Despite the limitations in this study, the researchers offered some clinically important implications concerning the management of patient symptoms and adherence to medication for patients with cancer. The sample consisted predominately of patients with breast cancer ($n$ = 17 of 23; $n$ = 3 with lung cancer) taking capecitabine, cyclophosphamide, and lapatinib. The researchers did not provide a rationale for the use of 100% as a determinant of good adherence in this pilot study.

Oakley, Johnson, and Ream (2010) conducted an ethnographic study and a feasibility study to understand the experiences of patients with cancer receiving oral chemotherapy and the feasibility of a generic patient diary for sustaining adherence to therapy. Four patients with

lymphoma receiving oral chlorambucil and five patients receiving therapy with oral capecitabine participated in the study. Core themes included self-medication and symptom management and self-efficacy. Patients found the diary helpful and useful, but found it would be more helpful if the diary was supported by a model of care to augment education and reiterate information. Both phases of the study were conducted at the same institution in the United Kingdom, and adherence to oral chemotherapy was not measured. It should be noted that capecitabine (Xeloda®, Genentech, San Francisco, CA) is an oral antimetabolite agent that is prescribed for patients with metastatic colon, breast, or renal cancer. When given as monotherapy, capecitabine is generally prescribed for 2 weeks, with one week off, for up to 6 months (8 cycles) of therapy, while oral EGFR inhibitors such as erlotinib may be given continuously for weeks to years (Xeloda® Package Insert).

Two studies examining adherence for patients with NSCLC receiving erlotinib therapy were found. Gebbia and colleagues (2011) published an abstract of a study to evaluate the impact of a treatment-monitoring intervention on adherence for patients with advanced NSCLC who received erlotinib as second-line therapy. The study was conducted in two cohorts: 1) a retrospective non-interventional phase monitoring 50 participants without a treatment management strategy; and, 2) a prospective interventional phase following 150 participants who received a treatment-management program, which included identification of a caregiver, patient and caregiver education and training about treatment and side effects of therapy, a calendar for follow-up visits, and a dedicated fax phone line to receive instructions or use of a fast-track visit system. Adherence was measured with the BAAS self-report tool, a visual analogue scale (VAS), pill counts, and missed appointments. During the first two months, adherence measured by BAAS > 95% was 72% for the first cohort, and 84% for the second cohort; by VAS, adherence

was 94% and 85% for the first and second cohorts, respectively. By pill count, adherence in the first two months was 78% and 87%, respectively. Mean adherence to study visits was 86% and 96%, respectively. Correlations between adherence and clinical outcomes were evaluated; the disease control rate, defined as complete response plus partial response plus stable disease, was 44% in the first cohort and 63% in the second cohort. A significant correlation was found between the number of adverse events and adherence ($r$ = .176, $p$ = .035). The abstract is the first published report addressing medication adherence for patients with NSCLC receiving oral targeted therapy; however, the socio-demographic characteristics of the participants, the rationale for the use of 95% as a cut-off for adequate adherence, and the theoretical underpinnings of the intervention were not reported.

Recently, a published report of an ongoing prospective observational cohort study (Timmers et al., 2011) was found. The study is examining 65 patients with NSCLC aged 18 years or older who have been initiating erlotinib therapy. Subjects are followed for up to 16 weeks. Adherence is measured at baseline and at 4, 8, 13, 16 weeks using MEMS and several questionnaires concerning adherence behavior (MARS), side effects (five point scale), dose adjustment, co-medication, quality of life (SF-12), and patient beliefs and attitudes toward medication and disease (the brief Illness Perception Questionnaire and the Beliefs About Medicines Questionnaire adjusted for erlotinib). Blood samples are drawn at 4, 8, and 16 weeks for plasma concentration of erlotinib. Taken together, the findings and limitations of these four studies imply that until medication-taking behavior is better understood, developing and testing theoretically-based interventions to enable patients with NSCLC need to proceed slowly.

### 2.3.4 Medication adherence and genetics for patients with cancer

The shift to the use of oral targeted therapies for treatment of cancer has in part led to an emphasis on personalized medicine, or the matching of patient genotype with the appropriate treatment for cancer (Thompson et al., 2011). The relationship and/or the implications for personalized treatment for cancer and medication adherence have yet to be explored. Lash and colleagues (2011) examined the relationship of CYP2D6 inhibition (*4 allele) and recurrence of breast cancer in a large case control population study in Denmark. Women who were registered with Denmark's Breast Cancer Cooperative Group and who were aged 35–69 years at the time of diagnosis of stage I–III breast cancer between 1985 and 2001 were examined for CYP2D6 genotyping and recurrence of breast cancer. In this patient sample, there was little to no association of those with one functioning allele, or no functioning allele, with recurrence of breast cancer. Adherence to tamoxifen was not an aim of the study, and the potential impact of adherence on breast cancer recurrence was not discussed.

Thompson and colleagues (2011) examined the association of CYP2D6 genotyping and recurrence of breast cancer in the context of adherence to tamoxifen in a large cohort of patients with breast cancer ($n$ = 618). Adequate adherence was defined as 80%, and was measured using a large prescription dataset. Adjusting for adherence to tamoxifen therapy increased the effect of CYP2D6 genotype on recurrence of breast cancer. The findings suggest that CYP2D6 genotype information may be helpful in determining who would most likely benefit from tamoxifen therapy. Similar studies examining patient genotype and adherence to oral targeted therapy were not found for patients with NSCLC taking an oral EGFR tyrosine kinase inhibitor.

### 2.3.5 Summary

In summary, a comprehensive review of the literature has demonstrated that (a) NSCLC is a deadly and costly disease with complicated and expensive treatment regimens, (b) EGFR tyrosine kinase inhibitors have unique side effect profiles and potential barriers to medication-taking including cost, (c) medication-taking behaviors for patients with chronic disorders receiving prescribed treatment regimens are well studied but difficult to apply to patients with NSCLC receiving EGFR tyrosine kinase inhibitors, and (d) medication-taking for patients with cancer has been studied primarily in women with breast cancer receiving hormonal therapy and individuals with leukemia taking imatinib. The knowledge learned is difficult to apply to individuals with NSCLC receiving EGFR tyrosine kinase inhibitor therapy due to the pathway-specific nature of the medications, as well as the unique side effect profiles. Limitations to this research include samples of mostly women, younger age, and side effect profiles of hormonal targeted agents that are significantly different than those of oral EGFR inhibitors. Suggestions for adherence management have not been well studied in patients with cancer, and studies examining medication-taking behaviors in patients with NSCLC taking oral targeted therapy were not found. One report of a pilot study evaluating a theory-based adherence intervention in patients with cancer was identified, but generally, studies of medication adherence in patients with cancer have not been theory-driven.

Therefore, examining the process of medication-taking in patients with NSCLC undergoing oral EGFR inhibitor therapy is timely, appropriate, and important. Exploratory research is needed to begin to develop the appropriate theoretical foundation to direct future investigations of adherence to cancer therapies, suggesting that qualitative, grounded theory

approach to examining the process of medication-taking of oral EGFR inhibitors (once chosen for treatment) is needed to address the identified gaps in the literature.

## 2.4 SIGNIFICANCE AND INNOVATION

Based on the review of the literature, this is the first study to describe the process of medication-taking in patients with NSCLC who are prescribed oral targeted therapy. The examination of the process of medication-taking of oral EGFR inhibitor therapies for patients with NSCLC is significant and timely. Research has shown that novel therapies like oral EGFR inhibitor therapies can increase survival and improve QoL for patients with NSCLC; however, oral targeted therapies are a new technology with limited understanding of the implications for medication-taking. Cost, different side effect profiles, complicated regimens, and changing dose protocols may be important factors affecting medication-taking. Furthermore, patients with NSCLC have greater gender and ethnic diversity than published breast cancer studies of adherence and are older in age than published studies of individuals with CML taking imatinib therapy. This dissertation is timely as it has addressed the missions of the American Cancer Society and the National Institute for Nursing Research, specifically, the promotion and improvement of the health of individuals, families, communities, and populations, and is a research priority for the Oncology Nursing Society.

## 2.5 PRELIMINARY STUDIES

Prior to the comprehensive exam and overview process, we conducted two pilot studies that were designed to answer research questions concerning medication-taking and adherence while developing the skills needed to perform qualitative and quantitative research. The first is a qualitative study that examines medication-taking and women with early stage breast cancer who were taking oral hormonal therapy with anastrozole. The second is a quantitative secondary analysis examining pre-treatment predictors of adherence to oral hormonal therapy for women with early stage breast cancer. The second manuscript is in draft form and will be finalized after the dissertation defense.

### 2.5.1 Pilot Study #1—Keeping the boogie man away": Medication self-management among women receiving anastrozole therapy

The impetus for this study stemmed from a discussion with the principal investigator of an ongoing study examining anastrozole therapy and cognitive function in women with early stage breast cancer. In that study, adherence is assessed continuously using the Medication Event Monitoring System (MEMS) (AARDEX, Ltd.), a bottle cap fitted with a microprocessor that records the date and time the cap is removed from a standard medication vial. It was noted that the MEMS cap records daily pill discharge, but the data do not provide information about how the women actually take their medication. Thus, the narrow concept of adherence for patients with cancer and the absence of research examining how women with breast cancer think about and take their medication left a gap in information necessary to develop and test interventions tailored to their needs. From 2009 to 2012, under the guidance of my mentors, we developed a

qualitative descriptive companion study to a larger cohort study (Cognitive Impairment Related to Anastrozole Use in Women; NCI 1 R01 CA 107408-01; Bender, PI; IRB0409010) to gain hands-on research skills through participation in their ongoing funded research. This manuscript was submitted to *Nursing Practice and Research* on June 11, 2012.

#### 2.5.1.1 Cover letter to *Nursing Practice and Research*

June 11, 2012

Annette DeVito Dabbs, PhD, RN, FAAN
Professor
University of Pittsburgh
School of Nursing
3500 Victoria Street
Pittsburgh, PA 15231

Dear Dr. DeVito Dabbs:

We are submitting a manuscript for review and possible publication in *Nursing Research and Practice*. The paper discusses the methods and findings for a qualitative study examining the medication-taking experiences for post-menopausal women with early stage breast cancer receiving anastrozole therapy. This manuscript has been reviewed and approved by all authors. The paper has not been submitted to any other journal; this work has not been published elsewhere.

Thank you for your consideration. If you need further information, please contact me by mail, telephone or e-mail at:

Karen Wickersham, PhD(c), RN
University of Pittsburgh
School of Nursing
440 Victoria Building
Pittsburgh, PA 15261
Telephone: 412-721-5899
E-mail: kew44@pitt.edu

Sincerely,

Karen E. Wickersham, PhD(c)
Doctoral Candidate
University of Pittsburgh
School of Nursing

#### 2.5.1.2 Abstract

The hormonal agent anastrozole improves clinical outcomes for women with breast cancer, but women have difficulty taking it for the five-year course. The unique medication-taking experiences related to self-management of oral hormonal therapy for women with early-stage breast cancer are not known. Our purpose was to describe the medication-taking experiences for post-menopausal women with early stage breast cancer who were prescribed a course of anastrozole therapy. Twelve women aged 58 to 67 years, midway through therapy, participated in audio-recorded interviews. Women's medication-taking experiences involved a belief in its importance and an imperative to take anastrozole. We found that women's side effect experiences, particularly menopausal symptoms, were significant, but only one woman stopped anastrozole due to side effects. Medication-taking included routinization interconnected with remembering/forgetting and a storage strategy. Some women noted a mutual medication-taking experience with their spouse, but most felt taking anastrozole was something they had to do alone. Our results provide insight into the way women with early-stage breast cancer manage their hormonal therapy at approximately the midpoint of treatment. Next steps should include examinations of medication-taking in socioeconomically and ethnically diverse patient samples, potential differences between pre- and post-menopausal women, and the effects of medication-taking on clinical outcomes.

#### 2.5.1.3 Introduction

Treatment of cancer has shifted to greater use of oral cancer agents [1], transferring responsibility for medication management to the patient. For post-menopausal women with early-stage breast cancer, therapy with oral aromatase inhibitors (AIs) like anastrozole has been shown to improve clinical outcomes [2]; however, women have difficulty taking their medication

for the generally prescribed five-year course. Oral AI therapy is a “chronic” care cancer treatment prescribed to prevent recurrence, but most women receiving this treatment do not have active cancer.

Self-management has been defined as one’s ability to manage symptoms, treatment, physical and psychosocial consequences and lifestyle changes fundamental to living with a chronic condition such as cancer [3]. For post-menopausal women with early stage breast cancer, self-management includes medication-taking with oral AI therapy, which requires women to perform complex activities, including identifying and counting pills, timing pill taking, obtaining and refilling prescriptions, generally for a period of five years [4]. Qualitative inquiry provides unique information concerning the medication-taking experiences for patients with chronic disorders [4-6], but little research has focused on the medication-taking experiences for patients with cancer. Ersek, Kraybill, and Du Pen [7] explored the reasons patients with cancer have trouble taking their pain medication; however, the purpose of analgesia is different from that of medication for prevention of recurrence of breast cancer. The two published studies examining medication-taking for patients with cancer have been conducted for children or adolescents with leukemia [8, 9], who have different issues related to medication-taking, including developmental concerns such as egocentrism, concrete thinking, and parental involvement [9]. Thus, our purpose was to describe the medication-taking experiences of post-menopausal women with early stage breast cancer who were receiving the oral hormonal agent, anastrozole. We sought to answer the question: “What are the experiences of women who take anastrozole therapy?”

#### 2.5.1.4 Methods

We used qualitative description to generate a complete narrative of the medication-taking experiences of women with early stage breast cancer taking anastrozole therapy [10].

***Parent study*** We accessed an existing sample and data from an ongoing study, The Anastrozole Use in Menopausal Women (AIM) Study, which examines the effect of anastrozole on cognitive function in women with early stage breast cancer ("The AIM Study"). The study includes postmenopausal women less than 75 years old who speak and read English and have completed at least eight years of education. Women are excluded for self-reported hospitalization for psychiatric illness within the last two years, prior diagnosis of other cancers and neurologic illness (e.g., stroke, multiple sclerosis, dementia syndrome), and distant metastases. Women are followed for their 5-year course of hormonal therapy. Adherence to anastrozole is assessed continuously using the Medication Event Monitoring System (MEMS) (AARDEX, Ltd.), a bottle cap with a microprocessor that records the date and time it is removed from a standard medication bottle. While medication adherence measures the end-result of medication-taking, access to The AIM Study participants allowed us a unique opportunity to answer our research question about the full scope of medication-taking behaviors in this sample.

**Current study** The "current study" reported here was a follow-up to The AIM Study. At the time we began our study (2009), most women in The AIM Study had completed at least six months of MEMS adherence monitoring. We conveniently sampled 12 post-menopausal women with early stage breast cancer from participants in The AIM Study.

**Procedure** The University of Pittsburgh Institutional Review Board approved the current study. We contacted 47 women enrolled in The AIM Study for whom we had complete six-month MEMS adherence data by mailings from The AIM Study PI to determine their interest in participating in the follow-up study. We interviewed all women who responded to the mailings. Interested women contacted the current study PI (KW), who then described the purpose of the interviews by telephone. The women provided written informed consent prior to the scheduled

interview, conducted at the participant's home ($n$ = 6) or at a convenient, private location ($n$ = 6). Sixteen interviews for 12 women were audio-recorded with observational notes for recording of the participant's non-verbal cues and eye contact [9]. Participants received $10 upon completion of the interview.

**Interviews** The PI (KW) performed in-depth, semi-structured interviews, averaging 30 to 40 minutes in length, using an interview guide of open-ended questions adapted from two previous qualitative studies of medication-taking [6, 11]. Questions included asking women about what it was like to take anastrozole, how and why they began taking it, how it made them feel, how it was different from their previous treatments, how they took it on a typical day and the strategies they used, what they found difficult about taking anastrozole, forgetting to take it, and who helped them. Interviews performed in a public place were shorter in duration, but not less informative, than those performed in the participant's home.

**Sociodemographic and clinical data** The following demographic and clinical data available from The AIM Study database were used to describe the sample. Sociodemographic information was collected using the University of Pittsburgh, School of Nursing, Center for Research in Chronic Disorders Sociodemographic Questionnaire. Women's depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II) [12]. Anxiety was assessed with the Profile of Mood States (POMS) Tension-Anxiety subscale [13]. Information concerning stage of breast cancer, tumor type, radiation therapy, and chemotherapy was abstracted from the patient medical record. Side effects of hormonal therapy were assessed with the Breast Cancer Prevention Trial (BCPT) Symptom Checklist [14, 15]. BDI-II, POMS, and BCPT data from The AIM Study 6-month and 18-month time points (closest to the interviews with the most complete data) were used for the analysis.

As another form of description of medication-taking of anastrozole, we categorized women according to their MEMS cap adherence rate: 100% adherers, good-adherers (90-99%), adequate-adherers (80-89%), and low-adherers (below 80%). These categories were established based on the literature focusing on various chronic disorders where 80% is generally good adherence and needed for disease maintenance [11, 16, 17]. We defined adherence as the percent of the prescribed doses taken. Women who discontinued or who were switched to another AI by their oncologist due to toxicities were included, as therapy discontinuation is an important variation (and consequence) of medication-taking.

**Data analyses** The current study PI reviewed each transcript while listening to the audiotape with observational notes for accuracy and for an understanding of the participant's focus. All interviews were transcribed and entered in a word document and in Atlas.ti (6.2.27) to manage and organize the data. Observational notes were summarized and included with each transcript. We developed a timeline for each woman outlining the timing of her breast cancer diagnosis, the start of anastrozole, and the side effects she experienced after beginning anastrozole to gain a sense of her overall experience with this treatment. As analysis progressed, interview language was refined for clarity. Probes were added concerning forgetting to take medication (e.g., "How did you realize you forgot?"), unexpected events that affected medication-taking (e.g., vacation/travel), and information received at therapy initiation (e.g., "What were you told about Arimidex®?").

Qualitative content analysis [18] was the primary method for data analysis. For each interview, the current study PI examined the data line by line to label (open code) text related to the woman's medication-taking experiences, using the interview questions as a guide. Similar codes were grouped into categories, which were examined for central themes. Dimensional

analysis was applied to themes to detect variations, specificity, and range [19]. Matrices were constructed for comparison and pattern recognition of participant characteristics (sociodemographic, breast cancer type and treatment, adherence level), side effects, depressive symptoms, and anxiety merging qualitative data and quantitative measures (BCPT, BDI-II, POMS). Numerical counts were used to characterize the strength of the main themes and subthemes within each case [20]. In this report, we use "most" to describe occurrence of a theme in at least nine women. Turning points in the analysis included the realization that medication-taking occurred despite side effect presence and severity and the pervasiveness of fear of breast cancer recurrence. Sampling, interviewing, and analysis continued until we reached informational redundancy, i.e., no new themes or patterns were recognized (n = 9); at that time, we enrolled three women for further sample diversity and to confirm existing findings. No new themes emerged and we achieved informational redundancy, but we cannot claim full saturation due to limited access to low-adherers and women who discontinued therapy.

We implemented the following steps to assure the trustworthiness of the data, analysis, and research process: a) A Co-Investigator (MBH) with expertise in qualitative methods and medication-taking research [6] audited the data to ensure the credibility of the analysis. b) Weekly group analysis meetings were conducted to discuss data exemplars, coding, and analytic decisions among all investigators. c) Four follow-up telephone interviews were performed to further clarify developing themes. For example, when several women mentioned that they had friends or relatives who were prescribed anastrozole and were no longer taking it, a follow-up question was added to further explore this experience and key informants were re-contacted to clarify this theme. d) All interview data, notes, and memos were documented using Atlas.ti (6.2.27) (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) software.

### 2.5.1.5 Results

***Participant characteristics*** Twelve women, aged 58 to 67 years, answered the mailings and were interviewed between June 2009 and April 2010. All women were white and well educated, and were similar to the women who participated in The AIM Study (Table 3).

**Table 3: Participant sociodemographic, breast cancer, and breast cancer treatment characteristics**

| Characteristic | Current study participants (*n* = 12) | The AIM Study participants (N = 162) |
|---|---|---|
| Age (in years) *Mean* | 62.5 | 60.1 |
| Years of education *Mean* | 14.8 | 15.1 |
| Marital status *n (%)* | | |
| Married | 6 (50.0) | 109 (67.3) |
| Divorced | 2 (16.7) | 20 (12.3) |
| Never Married | 3 (25.0) | 18 (11.1) |
| Widowed | 1 (8.3) | 13 (8.0) |
| Ethnicity *n (%)* | | |
| White | 12 (100.0) | 159(98.1) |
| MEMS 6-month adherence % | 87.8 | 88.7 |
| Breast Cancer Treatment *n (%)* | | |
| Radiation therapy | 11 (91.7) | 32 (19.8) |
| Mammosite therapy | 1 (8.3) | 12 (7.4) |
| Chemotherapy with anastrozole | 2 (16.7) | 25 (15.4) |

Note. MEMS = Medication Event Monitoring System (AARDEX, Ltd.)

Eleven women had been taking anastrozole for two and one-half to three years at the time of the interview. One woman discontinued anastrozole after six months, and was then switched to another AI by her oncologist due to arthralgias. At the time of her interview, she had discontinued all AI therapy due to side effects. Women in the current study had 6-month adherence levels ranging from 38.4% to 100% (mean = 87.8%), which were similar to women participating in The AIM Study (mean = 88.1%).

In their interviews, the women shared their perceptions about anastrozole ("what I think"), their experiences with side effects and side effect severity ("how it makes me feel"), and their day-to-day self-management of anastrozole ("what I do"). These three main topical categories describe their engagement in self-management of anastrozole and represent key

dimensions of self-management in this early phase of breast cancer survivorship. These categories involved an overarching belief in the importance of anastrozole, as well as an imperative to take it. We found that though the women's side effect experiences were significant, only one woman stopped taking anastrozole due to side effects. The women's day-to-day medication-taking experiences with anastrozole incorporated physical, temporal, and social aspects which women described as an individual responsibility or a social enterprise.

### *"Keeping the boogie man away": Importance of taking oral hormonal therapy*

All women assigned a sense of the value, purpose, or importance to anastrozole that offset other challenges associated with managing anastrozole, including side effect severity. The importance of anastrozole was defined as a woman's awareness or beliefs about therapy, the value, benefit, or relative worth of taking anastrozole, and her commitment or motivation to take anastrozole. Most women reported that side effects from anastrozole would not deter them from taking anastrozole therapy.

> I still take it. I still take it . . . if I thought that the medication was going to make me have early- onset dementia, I would think about it more, and I do know there've been some thoughts about that, but I still take it. I don't want to, (lowers tone) get breast cancer again, so, I take it.

Most women used imagery rather than the term "cancer recurrence" when discussing their beliefs and motivation to take anastrozole: "I'm taking it to keep the boogie man away." Another took it to keep "loose cells [from] traveling where they shouldn't." Another woman said, "That's very important, that pill . . . I want to live . . . I want to stay healthy." One participant with 100% adherence described a heightened consciousness about the role of anastrozole:

> I was conscious of saying, 'Okay, do your job in there, Arimidex.' . . . it was a funny thing. I didn't experience that in the first year and maybe only because I

> was experiencing those other things [side effects]. But, there was this short period of time where I'd take my water, drink it down and say, 'Okay, do your thing, Arimidex, get in there, kill any cells that you see . . .'

Conversely, two women implied nonchalance toward taking anastrozole and indicated that it was "no big deal" to take or to miss a dose of anastrozole. One woman stated, "Well, if I miss a day, it's not a big deal." The second woman described her views of missing a dose versus the medication's importance, incorporating imagery:

> So I think if you're taking Arimidex over years, they're [adrenal glands] not going to all of a sudden, if you miss one, they're not going to all of a sudden get back going again when they've been put to sleep as . . . for as long as they have been . . . I mean if you skipped a whole month . . . or even a whole week . . . that might be a different story . . .' cause then they'd start getting their act back together.

Although all women recognized the value of taking anastrozole, some interviews suggested tension between the desire to prevent cancer recurrence and uncertainty about taking anastrozole. This woman's comments further revealed ambiguity regarding the value of the medication in preventing cancer recurrence:

> To me, the benefit of not getting cancer, whether it's breast or some other site, is certainly more advantageous than putting up with a little bit of wrinkles or some other problem . . . but on the other hand, you wonder.

Women further indicated that there was a necessity or obligation to take anastrozole that went beyond their belief in its importance. This treatment imperative included her commitment to the program and "wanting to get to the finish line." The imperative was self-motivated, "I would never dream of quitting" "I truthfully want to do the five years. I want to complete the program as is," or externally motivated from a relative, a friend, or a health care provider, "My mom . . . would push me to take it and say 'you need to continue on this.'" Several women mentioned the imperative to take anastrozole "on doctor's orders." "He told me that I'd have to take it, and so I took it."

***Being thrown back into menopause: Side effects and side effect severity*** For all women, the opening question ("Tell me about your experience taking anastrozole") led, without prompting, to a description of the side effects of anastrozole. All women immediately described their challenges with hot flashes and associated sleep disturbances, arthralgias, fatigue, "female things", weight gain or loss, and their struggles with forgetfulness or memory loss, regardless of their MEMS cap adherence level. The women described the timing of when side effects occurred in relation to starting anastrozole (e.g., within a few months or right away), the time of day the side effects occurred, and the duration of the side effects (e.g., lasting a few minutes). They described how the side effects affected their daily life or altered their lifestyle, characterization (e.g., "like a torch"), frequency (e.g., occurring every few hours), and their attribution that the side effect was due to anastrozole, another therapy, or a process such as aging. One woman experiencing menopausal-like symptoms stated anastrozole "threw me back into menopause." Another characterized her hot flashes:

> Overall it feels like a torch . . . the chest area and face and forehead; my forehead's like soaking wet now . . . they come on real fast and last about a minute or two . . . during the night I might wake up it seems every two hours . . . like at midnight, two o'clock, four o'clock, six o'clock, and you know it wakes me up and sometimes I can't go back to sleep so that is an additional problem.

One woman who took anastrozole in combination with chemotherapy described her experiences with memory problems:

> The only thing I do have a problem with, and I have noticed it, is my memory. Now I'm remembering a lot of things . . . today, talking to you, but if somebody said, 'Well, I told you that yesterday,' or 'Don't you remember I . . .' 'I can't remember.' I have to really think, and that scares me. I mean I had a bad memory before (laughs) . . . but it, it is worse. It is, it is worse.

The woman who discontinued AI therapy due to hip pain described her experiences and the related uncertainty of the underlying cause of her pain:

> I think once you have cancer you start to think, 'Is this mets to the bone, or is this mets somewhere else . . . or is it a side effect from the medication'…when I take medication, I try not to read the side effects unless I'm having problems and then I go to the side effects and say, 'Ah, yeah, maybe this is it.' But when I started . . . in my hips, and it was at night and I was having trouble sleeping, I just decided that . . . this [anastrozole] wasn't for me.

To further explore the problem of the women's side effects and side effect severity, we constructed profiles of side effects for each participant by combining those side effects reported in interviews with information from the BDI-II, POMS, and BCPT (Table 4).

**Table 4: The women's self-reported side effects**

| ID | Hot flashes | Arthralgias | Sleep distur-bance | Fatigue | Weight gain or loss | Anxiety / Depressive symptoms | "Female things" | Cognitive problems |
|---|---|---|---|---|---|---|---|---|
| 1 | B | Both | | I | B | BDI-II, P | | B |
| 2 | | Both | I | | B | BDI-II, P | Both | Both |
| 3* | | Both | | | B | BDI-II, P, I | BCPT | I |
| 4 | Both | | I | | B | BDI-II, P | Both | B |
| 5 | B | | | | Both | BDI-II, P | | B |
| 6 | Both | B | I | | | BDI-II, P | B | B |
| 7 | Both | B | | | B | BDI-II, P | B | B |
| 8 | Both | B | I | I | Both | BDI-II, P | | Both |
| 9 | Both | B | I | I | B | BDI-II, P | | B |
| 10 | Both | Both | I | | | BDI-II, P | B | B |
| 11 | B | Both | | | B | BDI-II, P | B | B |
| 12 | Both | Both | I | I | | BDI-II, P | | Both |

Note. Arthralgias were defined as aches, pains, and joint pains. "Female things" were defined as vaginal itching, vaginal bleeding, vaginal discharge, or pain with intercourse.
B = Symptoms reported by the participant on the Breast Cancer Prevention Trial (BCPT) Symptom Checklist only
I = Symptoms reported by the participant during the interview only.
Both = Symptoms reported by the participant in both the interview and the BCPT.
P = Anxiety reported by the participant in the Profile of Mood States (POMS) Tension-Anxiety Subscale
BDI-II = Depressive symptoms reported by the participant in the Beck Depression Inventory-II Scale
* = This participant was the only woman to specifically express depressive symptoms or anxiety in her interview.

Participants reported three to six side effects; most women ($n$ = 10) reported five or more side effects. The two women classified as "low-adherers" reported the same type and number of side effects as the two 100% adherers. The woman who discontinued AI therapy due to side effect severity was classified as a "good" adherer and reported the same five side effects as the other women. Women expressed varying levels of depressive symptoms and anxiety when

completing the BDI-II and POMS surveys, but only one expressed these symptoms during her interview, and her scores did not indicate depression or anxiety. This mixed data analysis revealed no patterns between symptom number, type, and severity and adherence category.

Women also described the strategies they used to treat their side effects (e.g., pharmaceuticals, physical therapy), as well as daily management or compensation strategies. For example, one woman avoided or limited her activities, while another wrote down tasks or names to remember them. The woman with "summertime blues" described how she compensated for her memory and word-finding problems:

> I've worked with lots of women, and we all say (laughter) estrogen, the menopausal breakdown. But, I have days when I just . . . can't remember things like names or specific words for thoughts . . . And I'm usually really good. I love words, and I'm usually pretty good with them. But, I just have days when I can't, and I'm not as articulate . . . I just finished helping with the summer camp and we had about 18 college counselors . . . I remembered all their names, and once in a while I'd completely blank . . . but I had a notebook, I had my cheat sheet.

### *Doing it yourself: medication self-management*

**Physical** All women described in detail the actual hand-to-hand, tangible characteristics of taking anastrozole. Many women mentioned that the pill was tiny and easy to swallow. However, when anastrozole was packaged in blister packs for a short time (e.g., a few months), the women expressed extreme difficulty and irritation with opening the blister pack. One woman described receiving two three-month supplies of anastrozole packaged in blister packs:

> . . . My husband had to get them out . . . Arimidex people ought to know that that is not acceptable. (Laughter) Maybe they found that out . . . but I'll tell you that was the only time that I considered stopping. Because I have arthritis in my hands . . . and they're old hands. . . it was very, very difficult. I couldn't put it through, you know, so I tried to use a penknife, I tried to flip up the little foil thing . . . and sometimes I'd try to slice off the bubbles like this. (Gestures). It's just hard. I couldn't do it.

**Temporal** Central to self-management of anastrozole for all of the women was the routinization or integration of anastrozole into their everyday lives as anastrozole-taking became a consistent, accepted, or habitual medication self-management practice. They described timing anastrozole administration with meals or other medications, associating it with a visual cue (e.g., seeing the bottle on the window sill), a central location (e.g., kitchen), or a storage strategy (e.g., weekly pill minder). Women stated that participation in The AIM Study helped to routinize their medication-taking practice. Most ($n$ = 11) were already taking other prescription medications, vitamins, or supplements and incorporated anastrozole within their established routine.

Associated with routinization was remembering/forgetting to take anastrozole and their realization, reaction, and strategies for taking anastrozole after forgetting a dose:

> I was in that AIM Study and I had the little bottle, and I swear I took it every day, but there was a few times when she (study nurse) put it on the little machine to see that I had missed it a few times. Now last night I went to bed and I remembered about 1:00 [AM] and I came down the steps and took it.

Frequently, remembering was linked to a certain time of day or a storage strategy, such as a weekly pill container. For example, one woman stated she did not forget to take her anastrozole "'Cause I take it with my morning vitamin, my calcium, and fish oil." Another woman described:

> When I started it, that's when I put into my day [pill minder] . . . I've had no trouble remembering to take it, and that seems to be a good time [after supper] since its after my work day, except when I have a meeting, I don't forget.

Although women felt they remembered to take anastrozole, over half stated they occasionally missed a dose, only realizing it when noticing the pill was still in the container or her pocket, or when the MEMS cap was downloaded. Both low adhering women discussed the management of their missed doses in a similar manner.

> Sometimes I might play the 12 hour shuffle if I know I didn't take it the night before . . . maybe I'll take it in the morning, and then at bedtime, so it's probably putting two in one day, but trying to spread them apart, so it's not quite the same.

**Social** Some women described medication-taking as a social or a "mutual medication-taking" experience, referring to taking anastrozole at the same time a spouse or other family member took their own medications. Several women mentioned they had friends or relatives who were prescribed anastrozole and were no longer taking it. They denied that this deterred them from taking their own anastrozole. Most women described a "solitary" experience in which no one can or needs to help with taking anastrozole. A woman who lived alone stated, "I just have to do it." Another stated, " . . . I don't think he [husband] thinks about me taking my medication at all."

Women were told by their health care provider (HCP) to take anastrozole daily, but were given no other instructions. They expressed willingness to discuss their side effects with their oncologist or HCP; however, they were rarely asked about their experiences. In some cases, they received conflicting advice from HCPs. When discussing her foot pain, one woman indicated, "Foot doctor says no [unrelated to anastrozole]. Everyone else says 'Ah, yeah.'"

#### 2.5.1.6 Discussion

Our purpose was to describe the medication-taking experiences of post-menopausal women with early stage breast cancer who were receiving anastrozole therapy. The women's engagement in the self-management of their anastrozole involved a predominant belief in the importance of anastrozole, as well as an imperative to take it. We found that though the women's side effect experiences were significant, only one woman stopped taking anastrozole due to side effects. All medication-taking practices included routinization that was interconnected with remembering/forgetting to take anastrozole and a storage strategy (e.g., pill minder). Some

women noted a mutual medication-taking experience with their spouse, but most felt that taking anastrozole was something they had to manage alone.

Little research has addressed the beliefs about therapy for women with breast cancer receiving anastrozole therapy. For example, The ATAC Trialists' Group [2] found that fewer women withdrew from therapy with anastrozole when compared to tamoxifen, but the reasons for discontinuation were not reported. In the current study, all women, particularly those classified as adequate- and low-adherers, mentioned in some way the importance of taking anastrozole, in some cases referring to it as "no big deal." The use of personification in many of the women's speech is further evidence of the value and power that the women assigned to anastrozole.

In a qualitative comparison of 13 stroke patients who were classified as high- and low-adherers, Chambers and colleagues [21] found that both groups reported intentional and non-intentional adherence. Although some low-adherers in Chambers' [21] study reported occasionally skipping a medication, stability of a medication routine and beliefs about medication were central themes describing medication self-management in our sample. Pound and colleagues [22] discussed in a metasynthesis of qualitative studies of lay medication-taking experiences that few studies focus on those who reject their medications or take their medications without questioning. Our results suggest that those who take anastrozole without question may do so because they believe in the medication's value and importance.

The side effects the women reported were consistent with reports of menopausal symptoms induced by breast cancer treatment [23, 24], as well as with previous qualitative research describing women's experiences with hot flashes, the impact on daily life, and the higher priority that women placed on breast cancer treatment over menopausal symptoms [24-

27]. Garreau and colleagues [28] found that women receiving AIs switched therapy more often (47.5%) than those taking tamoxifen (37%). Salgado and Zivian [29] found that 30% of women discontinued AI therapy; of those, 84% discontinued due to side effects.

Given these findings, we would have expected women in the current study to describe switching or discontinuing AI therapy more often, but 11 of 12 women indicated that side effects did not deter them from taking anastrozole. The fact the women who were lower-adherers reported the same type and number of side effects as those who were 100% adherers is interesting and suggests that side effects related to AI therapy are significant to women midway through treatment. The impact of side effects on the medication-taking process with AI therapy for breast cancer prevention requires further examination. It is possible that completion of the BCPT, POMS, and BDI II surveys may have primed the women to describe the side effects that they felt were the most important, most persistent, and/or most present.

Self-management of anastrozole included physical, temporal, and social aspects of taking medication interwoven with remembering and forgetting. This is consistent with research examining medication-taking for patients with chronic conditions [4, 5, 30, 31]; however, in the current study, mutual-medication-taking went beyond social support, or reminding or assisting patients with their medications [4]. Rather, it included a partnership with a spouse in the physical taking of anastrozole that was part of her daily routine. Furthermore, self-management of medications often involves coordination between the patient and the health care team. In the current study, several women expressed taking anastrozole “on doctor’s orders,” but the women reported receiving little else in the way of instructions concerning medication use, side effects, and daily management of anastrozole.

The most significant limitation in the current study is the potential influence of participation in The AIM Study. The women who participated in the interviews were neither naïve to research nor to anastrozole adherence, which may have affected their responses. We interviewed all women who responded to the mailings, but most of them were already successful in self-management of anastrozole. Women may have had difficulty recalling their early experiences taking anastrozole, or they may have been primed to discuss side effects due to the recent completion of The AIM Study surveys. All women in the current study were white and well educated. Racial/ethnic disparities in treatment may affect self-management of medication and should be investigated.

The women in the current study were all approximately midway through their five-year course of therapy; therefore, they may have been more established in their medication-taking routines and less likely to discontinue anastrozole therapy. Interviewing women at earlier points in their treatment may help elicit the full scope of how side effects of hormonal therapies affect medication-taking. While we reached information redundancy in our sample, we did not saturate with regard to those who were low-adherers or who had stopped AI therapy. We were able to interview one participant who had discontinued anastrozole; however, we may have missed women at the beginning of their treatment who discontinued or were switched to other AIs. Nonetheless, our results provide insight into the way women at approximately the midpoint of their hormonal therapy manage their medications, and thus may inform interventions that would aid them in completing the full five years of anastrozole therapy.

#### 2.5.1.7 Conclusion

The women's experiences suggest several implications for medication self-management. Given that women were offered minimal information about taking anastrozole therapy, provision of

information about anastrozole, its side effects, and how and when to take it may be beneficial, beginning with the first clinic visit with ongoing reassessment at subsequent clinic visits. Second, while most women indicated they experienced similar side effects, the trajectory of those side effects differed among the women. This suggests that ongoing side effect assessment is needed even after therapy is well established. Finally, questions focusing on the patient's medication-taking experiences as a whole, rather than an overall verbal assessment of adherence, may prompt further discussion, including why they do or do not take their medication.

Our study offers a unique perspective into the medication-taking experiences of postmenopausal women with early stage breast cancer who were midway through a course of anastrozole who were successful at self-management of anastrozole therapy. While reports examining the end result of self-management of medication have been published, reports of research explaining how women view their experiences taking oral hormonal therapy are lacking. Our results help explain why women, regardless of their measured adherence level, take anastrozole therapy without question and continue despite the side effects of anastrozole. Next steps should include examinations of medication-taking concerning: a) socioeconomically and ethnically diverse patient samples; b) potential differences between pre- and post-menopausal women, particularly side effect severity and medication-taking; c) effects of medication-taking on clinical outcomes; and, d) women with breast cancer taking oral targeted therapies.

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**2.5.1.9 References**

1. Aisner, J. (2007). Overview of the changing paradigm in cancer treatment: Oral chemotherapy. *American Journal of Health-System Pharmacists, 64*(Supp 5), S4-S7. doi: 10.2146/ajhp070035
2. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) Trialists' Group. (2002). Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *The Lancet, 359,* 2131-2139. doi: 10.1016/S0140-6736(02)09088-8

3. Barlow, J., Wright, C., Sheasby, J., Turner, A., & Hainsworth, J. (2002). Self-management approaches for people with chronic conditions: a review. Patient Education and Counseling, 48, 177-187.

4. Russell, C. L., Kilburn, E., Conn, V. S., & Ashbaugh, C. (2003). Medication-taking beliefs of adult renal transplant recipients. *Clinical Nurse Specialist, 17*(4), 200-208.

5. Chen, C. -H., Wu, J. -R., Yen, M., & Chen, Z. -C. (2007). A model of medication-taking behavior in elderly individuals with chronic disease. *Journal of Cardiovascular Nursing, 22*(5), 359-365. doi: 10.1097/01.JCN.0000287029.87746.58

6. Erlen, J. A. & Happ, M. (2006). Patients with Alzheimer's disease who live at home: The challenge of medication taking. Podium presentation presented at the18th Scientific Sessions of the Eastern Nursing Research Society, Philadelphia, PA.

7. Ersek, M., Krapbill, B. M., & Du Pen, A. (1999). Factors hindering patients' use of medication for cancer pain. *Cancer Practice, 7*(5), 26-232.

8. Landier, W., Hughes, C. B., Calvillo, E. R., Anderson, N. L. R., Briseno-Toomey, D., Dominguez, L., … Bhatia, S. (2011). A grounded theory of the process of adherence to oral chemotherapy in Hispanic and Caucasian children and adolescents with acute lymphoblastic leukemia. *Journal of Pediatric Oncology Nursing, 28*(4), 203-223. doi: 10.1177/1043454211409582

9. Malbasa, T., Kodish, E., & Santacroce, S. J. (2007). Adolescent adherence to oral therapy for leukemia: A focus group study. *Journal of Pediatric Oncology Nursing, 24*, 139-151. doi: 10.1177/1043454206298695

10. Carter, B. J. (1993). Long-term survivors of breast cancer: a qualitative descriptive study. *Cancer Nursing, 16*(5), 354-361.

11. Lewis, M., Colbert, A., Erlen, J., & Meyers, M. (2006). A qualitative study of persons who are 100% adherent to antiretroviral therapy. *AIDS Care, 18*(2), 140-148. doi: 10.1080/09540120500161835

12. Beck, A. T, Steer, R. A, & Brown, G. K. (1996). *Beck Depressive Symptoms Inventory-II*. San Antonio: The Psychological Corporation.

13. McNair, D., Lorr, M., & Droppleman, L. F. (1992*). EdITS Manual for the Profile of Mood States*. San Diego: EdITS/Educational and Industrial Testing Service.

14. Ganz, P., Greendale, G. A., Petersen, L., Zibecchi, L., Kahn, B., & Belin, T. R. (2000). Managing menopausal symptoms in beast cancer survivors: Results of a randomized controlled trial. *Journal of the National Cancer Institute, 92*, 1054-1064. doi: 10.1093/jnci/92.13.1054

15. Stanton, A., Bernaards, C. A., & Ganz, P. A. (2005). The BCPT Symptom Scales: A measure of physical symptoms for women diagnosed with ar at risk for breast cancer. *Journal of the National Cancer Institute, 97*, 448-456. doi: 10.1093/jnci/dji069

16. Osterberg, L. & Blaschke, T. (2005). Adherence to medication. The New England *Journal of Medicine, 353*, 487-497.

17. Partridge, A. H, Archer, L., Kornblith, A. B., Gralow, J., Grenier, D., Perez, E., … Muss, H. (2010). Adherence and persistence with oral adjuvant chemotherapy in older women with early-stage breast cancer in CALGB 49907: Adherence companion study 60104. *Journal of Clinical Oncology, 28*(14), 2418-2422. doi: 10.1200/JCO.2009.26.4671

18. Grandheim, U. H. & Lundman, B. (2004). Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Education Today, 24*, 105-112. doi:10.1016/j.nedt.2003.10.001

19. Schatzman, L. (1991). *Dimensional analysis: Notes on an alternate approach to the grounding of theory in qualitative research*. New York, NY: Aldine de Gruyter.

20. Sandelowski, M. (2001). Real qualitative researchers do not count: The use of numbers in qualitative research. *Research in Nursing and Health, 23*, 230-240. doi: 10.1002/nur.1025

21. Chambers, J. A., O'Carroll, R. E., Hamilton, B., Whittaker, J., Johnston, M., Sudlow, C., & Martin, D. (2011). Adherence to medication in stroke survivors: A qualitative comparison of low and high adherers. *British Journal of Health Psychology, 16*(3), 592-609. doi: 10.1348/2044-8287.002000

22. Pound, P., Britten, N., Morgan, M., Yardley, L., Pope, C., Daker-White, G., & Campbell, R. (2005). Resisting medicines: A synthesis of qualitative studies of medicine taking. *Social Science and Medicine, 61*, 133-155. doi: 10.1016/j.socscimed.2004.11.063

23. Harris, P. F., Remington, P. L., Trentham-Dietz, A., Allen, C. I., & Newcomb, P.A. (2002). Prevalence and treatment of menopausal symptoms among breast cancer survivors. *Journal of Pain and Symptom Management, 23*(6), 501-509. doi: 10.1016/S0885-3924(02)00395-0

24. Knobf, M. T. (2002). Carrying on: The experience of premature menopause in women with early stage breast cancer. *Nursing Research, 51*(1), 9-17.

25. Fenlon, D. R. & Rogers, A. E. (2007). The experiences of hot flushes after breast cancer. *Cancer Nursing, 30*(4), E19-E26. doi: 10.1097/01.NCC.0000281731.95113.a3

26. Knobf, M. T. (2001). The menopausal symptom experience in young mid-life women with breast cancer. *Cancer Nursing, 24*(3), 201-211.

27. Flanagan, J. M., Winters, L. N., Habin, K., & Cashavelly, B. & (2012). Women's experiences with anti-estrogen therapy to treat breast cancer. *Oncology Nursing Forum, 39*(1), 70-77.

28. Garreau, J. R., DeLaMelena, T., Walts, D., Karamlou, K., & Johnson, N. (2006). Side effects of aromatase inhibitors versus tamoxifen: The patients' perspective. *The American Journal of Surgery, 192,* 496-498. doi:10.1016/j.amjsurg.2006.06.018

29. Sedjo, R. L. & Devine, D. (2011). Predictors of non-adherence to aromatase inhibitor therapy among commercially insured women with breast cancer. *Breast Cancer Research and Treatment, 125,* 191-200. doi: 10.1007s10549-010-0957-6

30. Proulx, M., Leduc, N., Vanderlac, L., Gegoire, J. -P., & Collin, J. (2007). Social context, the struggle with uncertainty, and subjective risk as meaning-rich constructs for explaining HBP noncompliance. *Patient Education and Counseling, 68,* 98-106. doi:10.1016/j.pec.2007.05.014

31. Reid, M., Clark, A., Murdoch, D. L., Morrison, C., Capewell, S., & McMurray, J. (2006). Patient strategies for managing medication for chronic heart failure. *International Journal of Cardiology, 109,* 66-73. doi:10.1016/j.ijcard.2005.05.051

### 2.5.2 Pilot Study #2—Patient-, illness-, or treatment-related baseline predictors of nonadherence to oral hormonal therapy

This study provided training in quantitative methods and analysis and in-depth analysis of potential pre-treatment predictors of adherence for women with early stage breast cancer taking oral hormonal therapy. The manuscript is in draft form and is formatted for *Nursing Research*.

### 2.5.2.1 Cover letter to *Nursing Research*

November 1, 2012

Molly C. Dougherty, PhD, RN, FAAN
CB# 7460 Carrington Hall
School of Nursing
University of North Carolina
Chapel Hill, NC 27599-7460

Dear Dr. Dougherty:

We are submitting a manuscript for review and possible publication in *Nursing Research.* The paper discusses the findings of a secondary analysis of two longitudinal cohort studies. The analysis examines patient-, illness-, and treatment-related pre-treatment predictors of short-term nonadherence to oral hormonal therapy for women with early stage breast cancer. This manuscript has been reviewed and approved by all authors. The paper has not been submitted to any other journal; this work has not been published elsewhere.

Thank you for your consideration. If you need further information, please contact me by mail, telephone or e-mail at:

Karen Wickersham, PhD, RN
University of Pittsburgh
School of Nursing
440 Victoria Building
Pittsburgh, PA 15261
Telephone: 412-721-5899
e-mail: kew44@pitt.edu

Sincerely,

Karen E. Wickersham, PhD, RN
University of Pittsburgh
School of Nursing

### 2.5.2.2 Acknowledgements

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#### 2.5.2.3 Abstract

Background: Adjuvant treatment with hormonal therapy improves clinical outcomes for breast cancer, but women have difficulty adhering to the five-year regimen. Objectives: To explore pre-treatment predictors of short-term nonadherence to oral hormonal therapy for women with early stage breast cancer from the baseline assessment to six months post-treatment. Methods: A secondary analysis was performed using data collected from 198 women enrolled in one of two longitudinal cohort studies. Nonadherence was defined as the percentage of prescribed doses of hormonal therapy not taken during the first six months of therapy measured using an electronic medication event monitoring system. Information on predictor variables was measured at pre-treatment using self-report and medical record review. Linear regression analysis was performed to examine relationships between predictor variables and six-month nonadherence in a univariate manner to first identify candidate predictors variables at $p$ = .20 and then multivariately considering candidate predictors identified through stepwise and backward elimination regression methods. Results: Participants were white (98.3%), well educated (15.0 ± 2.9 years), and on average 59.1 ± 7.5 years of age. Mean nonadherence was 11.6%. Stepwise and backward elimination modeling algorithms identified the same set of predictors associated with six-month nonadherence and explained 11.0% of the variance (adjusted $R^2$ = .10, s = 0.27). Clerical/administrative primary occupation ($p$ = .015), ductal carcinoma in situ tumor type ($p$ =

.006), and higher weight concern scores ($p$ = .004) were jointly associated with nonadherence. Discussion: The findings suggest additional examinations of nonadherence concerning work and symptom burden and their relationship to nonadherence are indicated.

#### 2.5.2.4 Introduction

For women with breast cancer, adjuvant treatment with oral hormonal agents has been shown to improve clinical outcomes. Five years of tamoxifen, a selective estrogen receptor modifier (SERM), is prescribed for pre- and peri-menopausal women with hormone receptor positive, early stage breast cancer (Jonat, Pritchard, Sainsbury, & Klijn, 2006). Aromatase inhibitors (AIs), such as anastrozole, are superior to tamoxifen in reducing the risk of disease recurrence and contralateral disease in postmenopausal women (Newman & Singletary, 2007). Despite the clear therapeutic benefits of oral hormonal therapy, adherence, the "extent to which patients follow the instructions they are given for prescribed treatment" (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008, p. 2), remains challenging for women with breast cancer.

A number of patient-, illness-, and treatment-related factors have been shown to affect nonadherence to both tamoxifen and AIs but with varied results. For example, researchers have examined patient-related factors such as age and socioeconomic status (SES) and their relationships to nonadherence to tamoxifen therapy; however, both younger (< 45 years) (Kahn, Schneider, Malin, Adams, & Epstein, 2007; Partridge, Wang, Winer, & Avorn, 2003) and older women (> 65 to 85 years) (Barron, Connolly, Bennett, Feely, & Kennedy, 2007; Partridge et al., 2003) have been shown to be more likely to discontinue tamoxifen therapy than women ages 45 to 65. Partridge and colleagues (2003) found that "non-white" women were more likely to discontinue tamoxifen therapy than "white" women. Lebovits and colleagues (1990) found that women who discontinued oral chemotherapy had a significantly lower SES ($p$ < .02) than

women who continued their therapy; however, oral chemotherapeutic agents typically have different side effect profiles from those of oral hormonal therapies due to different mechanisms of action that could differentially affect adherence.

The relationships between other patient-related factors such as depression and anxiety and nonadherence to tamoxifen therapy are not well defined. Significantly higher tamoxifen nonpersistence (early discontinuation) rates have been shown for women who reported problems with mood (36%) versus women who reported no mood problems (12%) (Demissie, Silliman, & Lash, 2001). Use of antidepressant agents in the year before initiation of tamoxifen therapy has been associated with tamoxifen nonpersistence (Barron et al., 2007). Lebovits and colleagues (1990) found that women who discontinued self-administered chemotherapy had higher depressive symptom disturbances than women who did not discontinue therapy ($p < .05$). Nonetheless, depression and anxiety are related to nonadherence in individuals with chronic illness (Rubin, 2005) and in women at risk for breast cancer (Cohen, 2002).

Treatment-related factors such as higher breast cancer stage (stage II) (Lebovits et al., 1990) and prior chemotherapy (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman al., 2004) have been reported to be less associated with discontinuation of tamoxifen therapy. Positive hormone receptor status has ben associated with both ongoing tamoxifen use at four years (Kahn et al., 2007) and with stopping tamoxifen therapy by the second year (Fink et al., 2004). Partridge and colleagues (2003) found that women with mastectomy versus breast conserving surgery were more likely to be nonadherent to tamoxifen therapy. No published reports specifically examining women's menopausal status as a potential predictor of adherence to either tamoxifen or AIs were found.

Side effect severity and discontinuation of tamoxifen has been examined with mixed results. Fink and colleagues (2004) reported that side effects were not associated with discontinuation of tamoxifen; however, other researchers have reported that women who experienced side effects were more likely to stop taking tamoxifen (Demissie et al., 2001; Kahn et al., 2007). Grunfeld, Hunter, Sikka, and Mittal (2005) have reported that of those who discontinued therapy with tamoxifen, 46% discontinued due to side effects. Generally, hot flushes and night sweats were the primary concern.

Nonadherence or nonpersistence to AIs related to side effects has been evaluated mostly in the context of clinical trials. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial (2002), there were fewer women who withdrew from therapy with anastrozole compared to tamoxifen; however, higher nonpersistence rates with AIs were noted in similar trials comparing exemestane and letrozole with tamoxifen (Coombes, Hall, & Gibson, 2004; Goss, Ingle, & Martino, 2003). Younger age, out-of-pocket costs of greater than $30 US per AI prescription, no mastectomy, and higher co-morbid condition burden have been associated with 12-month nonadherence to AI therapy (Sedjo & Devine, 2011). In a qualitative analysis of the medication-taking experiences for women with early-stage breast cancer who were midway through a five-year course of anastrozole therapy (Wickersham, Happ, & Bender, under review; Wickersham, Happ, & Bender, 2011), most women (11/12) (91.7%) continued to take anastrozole due to a strong belief in its importance despite side effect severity.

Adherence to oral hormonal therapy for women with breast cancer remains difficult. Patient-, illness-, and treatment-related factors have been associated with adherence to oral hormonal therapy with tamoxifen and AIs but with inconsistent findings, and menopausal status was not reported. Further exploration of pre-treatment predictors of nonadherence to oral

hormonal therapies, including women's menopausal status (pre- or post-menopausal), may help identify women with early stage breast cancer who are at risk for nonadherence. Therefore, our aim was to explore pre-treatment patient-, illness-, and treatment-related predictors of short-term nonadherence to oral hormonal therapy for women with early stage breast cancer (Stage I, II, or IIIa) from the pre-treatment assessment (pre-hormonal therapy) to six months post-treatment. We hypothesized that (a) age and marital status are positively associated with nonadherence, and the number of years of education, employment status, and primary occupation are negatively associated with nonadherence. (b) Prior hormonal replacement therapy within the last three months, radiation therapy, and tumor type are negatively associated with nonadherence to hormonal therapy; women's menopausal status (pre- or post-menopausal), stage of breast cancer and treatment with chemotherapy are positively associated with nonadherence to hormonal therapy. (c) Perceived severity of side effects of hormonal therapy, depressive symptoms, fatigue, and anxiety are negatively associated with nonadherence for women with early stage breast cancer.

#### 2.5.2.5 Methods

This investigation was a secondary analysis of two longitudinal cohort studies: (a) *The Anastrozole Use in Menopausal Women (AIM) Study*, which examined the effect of anastrozole on cognitive function in women with early stage breast cancer and explores whether anastrozole adherence mediates cognitive function in this sample; and (b) *Predictors of Adherence to Hormonal Therapy in Breast Cancer* (The ONS Study), which examined the pattern of adherence, patient and illness/treatment predictors of adherence, and moderation effects between patient factors and illness/treatment factors to hormonal therapy in women with early stage breast cancer. The University of Pittsburgh Institutional Review Board approved both studies.

The ONS Study was guided by Christensen's (2000) Interactionalist Framework for Adherence, which posits that the interaction of patient factors with illness/treatment factors provide the main influence over adherence in persons with chronic illness.

***Setting and Sample*** The present analysis was performed on one combined dataset from the baseline (pre-initiation of adjuvant endocrine therapy) assessments from both The AIM and ONS Studies. Both studies assessed adherence in the same manner and had similar inclusion criteria; therefore, the two samples were combined into one dataset. Both studies included women less than 75 years who were able to speak and read English and who had completed a minimum of eight years of education. Women were excluded for self-reported hospitalization for psychiatric illness within the last two years, prior diagnosis of neurologic illness, distant metastases including the central nervous system, and prior diagnosis of cancer. Because The AIM Study focused on women who were receiving therapy with anastrozole, only post-menopausal women were included in the study; however, both pre- and post-menopausal women were enrolled into The ONS Study. Women who received oral hormonal therapy alone or in combination with chemotherapy were included in the present analysis.

***Variables and Measures*** Adherence to hormonal therapy was continuously assessed over the first six months of therapy with the Medication Even Monitoring System (MEMS) (AARDEX, Ltd.). The MEMS is a bottle cap fitted with a microprocessor that records the date/time the cap is removed from a standard medication vial. The MEMS cap records each medication-taking event, including patterns and timing of doses and allows for detection of missed and extra doses (Cramer, Scheyer, & Mattson, 1990). Nonadherence (dependent variable) was defined as the percentage of prescribed doses of hormonal therapy not taken during the first six months of therapy. For consistency with current literature concerning adherence for patients

with chronic illnesses, including patients with cancer, nonadherence was defined as < 80% (Osterberg & Blaschke, 2005).

**Patient-Related Variables** Patient-related factors assessed included sociodemographic variables, hormone replacement therapy (HRT) use in the last three months, depressive symptoms, anxiety, and fatigue. Sociodemographic variables included women's employment status, primary occupation, age, total number of years of education, HRT in the last three months, and marital status. Because the combined sample of women was 98.3% Caucasian, race/ethnicity was excluded as a predictor variable due its limited variability. Sociodemographic information was collected using the University of Pittsburgh, School of Nursing Center for Research in Chronic Disorders (CRCD) Sociodemographic Questionnaire.

Women's self-reported depressive symptoms were measured using the Beck Depression Inventory-II, a 21-item, self-report measure on which women rate depressive symptoms and attitudes on a four-point Likert scale (Beck, Steer, & Brown, 1996). The score is the sum of responses for items. The Cronbach's alpha coefficient for 500 outpatients with mental disorders was .92 and for 120 college students was .93. The BDI-II correlates strongly with the major depression episode portion of the Structured Clinical Interview for DSM-IV Axis I Disorders (.83) (Sprinkle et al., 2002; Stukenberg, Dura, & Kielcolt-Glaser, 1990) and the Revised Hamilton Rating Scale for Depression (.71) (Beck et al., 1996; Spreen & Straus, 1998).

Anxiety was assessed with the Profile of Mood States (POMS) Tension-Anxiety subscale, a 9-item, self-report subscale in which women's adjectives of heightened musculoskeletal tension (somatic and observable) are rated on a five-point Likert scale (McNair, Lorr, & Droppleman, 1992). The score is the sum of responses for items. Internal consistency was .92 and test-retest reliability was .70 in 1000 psychiatric outpatients (McNair et al., 1992).

The POMS is sensitive to changes in anxiety levels in patients with cancer (Cassileth et al., 1992). Fatigue was measured using the POMS Fatigue-Inertia subscale, a seven-item, self-report subscale in which adjectives of weariness, inertia, and low energy levels are rated on a five-point Likert scale (Mason, Matsuyama, & Jue, 1995). The score is the sum of responses for items.

**Illness- and Treatment-Related Variables** Information concerning stage of breast cancer, tumor type, radiation therapy, and chemotherapy was abstracted from the patient medical record. Women's menopausal status (pre- or post-menopausal) was determined using a combination of the women's natural menopause status at entry into each study and the MEMS-monitored medication. In the case where natural menopause status was missing, the MEMS-monitored medication (anastrozole, letrozole, extramestane, multiple AIs, or tamoxifen) determined the participant's menopausal status, since they are prescribed according to menopausal status.

Side effects of hormonal therapy were assessed with the Breast Cancer Prevention Trial (BCPT) Symptom Checklist, a self report measure of the degree that women are bothered by 43 treatment- and menopausal-related symptoms in the past four weeks (Ganz et al., 2000; Stanton, Bernaards, & Ganz, 2005). Women rate symptoms on a five-point Likert scale (0 = not at all to 4 = extremely). Eight-factor (Stanton et al., 2005; Terhorst, Blair-Belansky, Moore, & Bender, 2010) and seven-factor (Cella et al., 2007) structures have been reported for the BCPT. For consistency, the eight subscales used in The AIM Study were calculated in the present secondary analysis: vasomotor symptoms, gastrointestinal (GI) symptoms, bladder control, cognitive symptoms, weight concerns, musculoskeletal pain, gynecological symptoms, and dyspareunia. Subscale scores are the average score for items in each subscale, and the total score is the average score across all items. Cronbach's alphas for subscale scores range from .43 to .83 for

women with breast cancer receiving hormonal therapy. BCPT subscale scores are significantly related to scores on the SF-36 Physical Health and Mental Health subscales ($p$ = .05 to .001) (Alfano et al., 2006; Terhorst et al., 2010).

**Statistical Analyses** All statistical analyses were performed with IBM® PASW® Statistics v.19.0 (Armonk, NY). Descriptive statistics were performed to describe the data distributions and to characterize the study sample. The independent samples t-test (or Mann-Whitney U-test, if data were non-normal) and the Chi-square test of independence (or Fisher exact test, if cell sizes were sparse) were used to compare women in The AIM Study with women in The ONS Study at pre-treatment to investigate whether certain characteristics may be more associated with study membership. Data were screened for accuracy of input, univariate and multivariate outliers, missing data, multicollinearity and severe violations in the underlying assumptions for multiple linear regression. Linearity of continuous predictor variables was assessed by examining bivariate scatterplots. Participants with large amounts of missing data (e.g., entire BDI, POMS, or nonadherence values missing) were removed from the data set. For categorical predictors, sparsely populated categories were collapsed in a meaningful way to limit the sparseness of cells.

Multiple linear regression analysis was used to examine patient-, illness-, and/or treatment-related factors that predict short-term nonadherence to oral hormonal therapy for women with early stage breast cancer from the pre-treatment assessment (pre-hormonal therapy) to six months post-treatment. Statistical analyses for evaluation of the candidate predictors were completed in two stages. The univariate associations between each candidate predictor variable and the outcome variable (six-month nonadherence) were assessed using a cut-off of $p$ = .20. Those predictor variables meeting the criteria of $p$ = .20 were retained for further consideration in the multivariate analysis using multiple linear regression. The second stage of analysis

employed multiple linear regression analyses using both stepwise and backward modeling algorithms to identify the predictors of six-month nonadherence. Candidate predictors were retained if they remained associated at $p < .10$ in the multiple linear regression analysis.

Although the multicollinearity statistics were within acceptable limits for all variables, depressive symptoms, anxiety, and fatigue were highly correlated with each other. Thus, the potential for an interaction between depressive symptoms and anxiety were explored. An interaction variable was created using both the centered and un-centered values of depressive symptoms and anxiety. The interaction variable was then added to the baseline predictor model containing the main effects of predictors and assessed for the change in the model $R^2$ and the statistical significance of the added interaction term. Minimal change in $R^2$ was noted, and both were not statistically significant. When potential interaction variables were created for primary occupation, ductal carcinoma in situ (DCIS) tumor type, and weight concerns and tested in a similar fashion, no significant change to the stepwise model was noted; however, the backward elimination model demonstrated that primary occupation, weight concerns, and the interaction between primary occupation and DCIS tumor type were statistically significant.

#### 2.5.2.6 Results

A summary of the descriptive statistics for both the combined sample and by study (AIM or ONS) is provided in Table 5.

**Table 5: Sociodemographic characteristics of the combined sample of women**

| | **AIM Study (*n* = 162)** | **ONS Study (*n* = 36)** | **Combined Sample (*N* = 198)** |
|---|---|---|---|
| Age (in years) | | | |
| *Mean (SD)* | 60.6 (6.1) | 52.4 (9.5) | 59.1 (7.5) |
| Education (in years) | | | |
| *Mean (SD)* | 15.1 (3.0) | 14.8 (2.7) | 15.0 (2.9) |
| Marital status | | | |
| *n (%)* | | | |

| | | | |
|---|---|---|---|
| Never married | 18 (11.1) | 2 (5.6) | 20 (10.1) |
| Currently married | 109 (67.3) | 27 (75.0) | 136 (68.7) |
| Widowed | 13 (8.0) | 3 (8.3) | 16 (8.1) |
| Separated | 2 (1.2) | 0 (0) | 2 (1.0) |
| Divorced | 20 (12.3) | 4 (11.1) | 24 (12.1) |
| Ethnicity | | | |
| *n (%)* | | | |
| White | 159 (98.1) | 35 (97.2) | 194 (98.0) |
| African American | 3 (1.9) | 0 (0) | 3 (1.5) |
| Multi-racial | 0 (0) | 1 (2.8) | 1 (0.5) |
| Latino | 1 (0.6) | 1 (2.8) | 2 (1.0) |
| Employed | | | |
| *n (%)* | | | |
| Yes | 111 (68.5) | 27 (75.0) | 138 (69.7) |
| No | 51 (31.5) | 9 (25.0) | 60 (30.3) |
| Primary occupation | | | |
| *n (%)* | | | |
| Higher executive | 2 (1.2) | 3 (8.3) | 5 (2.5) |
| Medium-sized business, teacher, health care professional | 38 (23.5) | 7 (19.4) | 136 (68.7) |
| Administrative | 19 (11.7) | 5 (13.9) | 24 (12.1) |
| Clerical/sales | 2 (19.8) | 8 (22.2) | 40 (20.2) |
| Skilled-manual | 3 (1.9) | 2 (5.6) | 3 (1.5) |
| Non-skilled manual | 15 (9.3) | 2 (5.6) | 17 (8.6) |
| Unskilled | 2 (1.2) | 2 (5.6) | 4 (2.0) |
| Homemaker | 12 (7.4) | 0 (0) | 12 (6.1) |
| Disabled/student/ retired/no occupation | 39 (24.1) | 2 (5.6) | 41(20.7) |
| Menopausal Status | | | |
| *n (%)* | | | |
| Pre-menopausal | 0 (0) | 19 (52.8) | 19 (9.6) |
| Postmenopausal | 162 (100) | 17 (47.2) | 179 (90.4) |
| HRT last 3 months | | | |
| *n (%)* | | | |
| Yes | 20 (12.3) | 3 (8.3) | 23 (11.6) |
| No | 65 (40.1) | 4 (11.1) | 69 (34.8) |
| N/A | 7 (19.4) | 29 (80.6) | 92 (46.5) |
| MEMS-monitored medication | | | |
| *n (%)* | | | |
| Anastrozole | 162 (100%) | 7 (19.4) | 169 (85.4) |
| Letrozole | 0 (0) | 7 (19.4) | 9 (3.5) |
| Examestane | 0 (0) | 2 (5.6) | 2 (1.0) |
| Tamoxifen | 0 (0) | 19 (52.8) | 19 (9.6) |
| Multiple AIs | 0 (0) | 1 (2.8) | 1 (0.5) |
| Radiation Therapy | | | |
| *n (%)* | | | |
| Radiation | 32 (19.8) | 25 (69.4) | 57 (28.8) |
| Mammosite | 12 (7.4) | 0 (0) | 12 (6.1) |
| Chemotherapy | | | |
| *n (%)* | | | |

| | | | |
|---|---|---|---|
| Yes | 25(15.4) | 12(33.3) | 37(18.7) |
| No | 39(24.1) | 21(58.3) | 60(30.3) |
| Stage of Breast Cancer *n* (%) | | | |
| LCIS | 1 (0.6) | 0 (0) | 1 (0.5) |
| I | 119 (73.5) | 20 (55.6) | 139 (70.2) |
| IIa | 26 (16.0) | 9 (25.0) | 35 (17.7) |
| IIb | 9 (5.6) | 3 (8.3) | 12 (6.1) |
| IIIa | 7 (4.3) | 4 (11.1) | 11 (5.6) |
| Type of Tumor *n (%)* | | | |
| DCIS | 71 (43.8) | 8 (22.2) | 79 (39.9) |
| LCIS | 5 (3.1) | 2 (5.6) | 7 (3.5) |
| Infiltrating ductal | 142 (87.7) | 28 (77.8) | 170 (85.9) |
| Tubular | 6 (3.7) | 0 (0) | 6 (3.0) |
| Mucinous | 2 (1.2) | 0 (0) | 2 (1.0) |
| Infiltrating lobular | 14 (8.6) | 6 (16.7) | 20 (10.1) |
| Combination | 1 (0.6) | 0 (0) | 1 (0.5) |
| BDI Total Score | | | |
| *Mean (SD)* | 5.83 (5.6) | 6.68 (6.0) | 5.97 (5.7) |
| POMS Fatigue Total Score | | | |
| *Mean (SD)* | 6.22 (6.1) | 5.66 (6.0) | 6.01 (6.1) |
| POMS Anxiety Total Score | | | |
| *Mean (SD)* | 6.79 (4.5) | 6.47 (5.0) | 6.73 (4.6) |

Note. AI = Multiple aromatase inhibitors. DCIS = ductal carcinoma in situ. LCIS = lobular carcinoma in situ. POMS = Profiles of Mood State. BDI = Beck Depression Inventory-II. MEMS = Medication Event Monitoring System (AARDEX, Ltd.).

*Women may have more than one type of breast cancer tumor type. Participants with DCIS also had another tumor to be eligible for the parent studies.

Overall, the mean age of the women was 59.1 ± 7.54 years (range 39-75) and the mean number of years of education was 15.0 ± 2.91 (range 10-26). Overall, the mean nonadherence was 11.6 ± 23.3%. Women were similar between the studies in terms of self-reports of depressive symptoms, anxiety, fatigue, symptoms based on BCPT subscales, or adherence (transformed and untransformed). For The AIM Study, women were 13.2% nonadherent at six-months post-treatment, and women in The ONS Study were 4.6% nonadherent. We found an expected significant difference in age at baseline between the two groups, t(196) = 6.497, $p$ = .0001, given that only post-menopausal women participated in The AIM Study and were likely to be somewhat older than women in The ONS Study because the sample for that study was comprised of both pre- and post-menopausal women. As anticipated, the proportion of women being menopausal differed between the studies since only post-menopausal women participated in The AIM Study (Fisher's exact test $X^2$ =94.575, $p$ = .0001). Also since no women in The ONS Study received mammosite therapy, the distribution of the type of radiation therapy received also differed between the studies ($X^2$ =9.229, $p$ = .026). No other differences between the two studies were observed.

Candidate predictors identified through screening that were retained at $p$ = .20 are listed in Table 6.

**Table 6: Stepwise and backward elimination models with candidate predictors**

| Variable | Description | Sample Size (*N*) | Univariate Analysis | Multiple Linear Regression Analysis—Stepwise | | | Multiple Linear Regression Analysis—Backward Elimination | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | ***p*-value** | ***b*** | **SE** | ***p*-value** | ***b*** | **SE** | ***p*-value** |
| Age | Mean years | 198 | .266 | | | | | | |
| Education | Mean years | 198 | .511 | | | | | | |
| Married/ Partnered | Yes (0)/no (1) | 198 | .811 | | | | | | |
| Employed | Yes (0)/no (1) | 198 | **.074*** | | | | | | |
| Primary occupation | 1=high exec/medium manager<br>0=admin/clerical<br>2=semi-skilled/ non-skilled/ unskilled<br>3=homemaker/ student/disabled /retired | 191 | **.014*** | .171 | .017 | **.015**** | .171 | .017 | **.015**** |
| Menopausal status | Pre-/post-menopausal (0=post-, 1=pre-) | 198 | **.176*** | | | | | | |
| HRT in last 3 months | 0=yes, 1=no | 92 | .505 | | | | | | |
| Stage of breast cancer | 0=I<br>1=IIa, IIb, III | 198 | .880 | | | | | | |
| Type of tumor | | | | | | | | | |
| DCIS | Yes (0)/no (1) | 198 | **.008*** | .171 | .041 | **.006**** | .191 | .041 | **.004**** |
| Infiltrating ductal | Yes (0)/no (1) | 198 | .270 | | | | | | |
| Infiltrating lobular | Yes (0)/no (1) | 198 | **.088*** | | | | | | |
| Radiation therapy | 0=radiation<br>1=mammosite | 69 | .250 | | | | | | |
| Chemotherapy | 0=yes<br>1=no | 97 | .866 | | | | | | |
| Depression | BDI sum | 198 | **.139*** | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Anxiety | POMs sum | 198 | **.214*** | | | | | | |
| Fatigue | POMs sum | 198 | **.048*** | | | | | | |
| Vasomotor | BCPT subscale | 198 | .759 | | | | | | |
| GI symptoms | BCPT subscale | 198 | **.025*** | | | | | | |
| Bladder control | BCPT subscale | 198 | **.212*** | | | | | | |
| Cognitive symptoms | BCPT subscale | 197 | **.199*** | | | | | | |
| Weight problems | BCPT subscale | 198 | **.001*** | .199 | .038 | **.004**** | .199 | .038 | **.004**** |
| Musculo-skeletal pain | BCPT subscale | 198 | **.038*** | | | | | | |
| Gyne-cological | BCPT subscale | 198 | **.046*** | | | | | | |
| Dyspareunia | BCPT subscale | 198 | .288 | | | | | | |
| BCPT Total Subscale Score | | 198 | **.004*** | | | | | | |

Note. HRT = hormone replacement therapy; BCPT = Breast Cancer Prevention Trial Symptom Checklist; BDI = Beck Depression Inventory-II; POMS=Profile of Mood States; DCIS = ductal carcinoma in situ; b=unstandardized regression coefficient; SE=standard error of the unstandardized regression coefficient
0 = reference group
* = retained for multiple linear regression analysis $p < .20$
** = retained for multiple linear regression analysis $p < .10$
Stepwise: $R^2 = .114$ Adjusted $R^2 = .100$ s = .27910 $p < .0001$
Backwards Elimination: $R^2 = .123$, Adjusted $R^2 = .109$, s = .27765 $p < .0001$

Candidate categorical predictors of nonadherence included employment status, primary occupation, DCIS tumor type, infiltrating lobular tumor type, and menopausal status. Depressive symptoms, anxiety, fatigue, GI symptoms, bladder control, cognitive symptoms, weight problems, gynecological symptoms, musculoskeletal pain, and total BCPT score were identified as continuous linear predictors of nonadherence. Using stepwise multiple linear regression analyses of these candidate predictor variables, primary occupation ($p$ = .015), DCIS tumor type ($p$ = .006) and weight concerns ($p$ = .004) were identified as predictors of women's nonadherence at six months post treatment (Table 6). Backward multiple linear regression analyses performed in the same manner identified the same three predictor variables (Table 6). The backward elimination model was selected as the final model.

#### 2.5.2.7 Discussion

We examined potential patient-, illness-, and/or treatment-related factors and their relationship to short-term nonadherence to oral hormonal therapy for women with early stage breast cancer from the baseline assessment (pre-hormonal therapy) to six months post-treatment. We found that a backward elimination model best represented the data. Based on our findings, women with DCIS tumor type, whose primary occupation was clerical or administrative, or who had higher weight concern BCPT scores were associated with less adherence at six months post-treatment.

Previous reports of predictors of nonadherence to hormonal therapy with tamoxifen or AIs have not addressed employment status or occupation. Our results suggest that women with more burdensome workloads may be more likely to be nonadherent; however, further exploration is needed. In our analysis, we collapsed seven categories of primary occupations into four (high executive/medium level manager; administrative/clerical; semi-skilled/non-

skilled/unskilled; homemaker/student/ disabled/retired); it is possible that we lost information that may further explain our findings by using this technique.

We found that weight concerns were associated with nonadherence six months post-treatment, but no other symptoms were retained in either the stepwise or backwards-elimination models. Prior reports of the relationship between side effect severity and discontinuation of tamoxifen or AI therapy have been somewhat unclear. The types of weight concern side effects that women with breast cancer who are taking oral hormonal therapy have included attractiveness (Grunfeld et al., 2004), but this was not found to be a significant predictor of nonadherence. Other researchers have measured the severity of side effects (e.g., severe, moderate, mild, none) (Kahn et al., 2007) or the number of side effects (Lash et al., 2006), but we were unable to find specific reports regarding weight concerns and nonadherence for women with breast cancer taking oral hormonal therapy. Our findings are somewhat consistent with our qualitative analysis of medication-taking for women receiving anastrozole therapy (Wickersham, Happ, & Bender, 2011). In that study, women who were participants in The AIM Study provided rich description of their side effects of therapy, which included hot flashes, arthralgias, fatigue, sleep disturbances, and memory problems. Despite the severity of their symptoms, most (11 of 12 participants, 91.67%) indicated that their side effects would not stop them from taking their anastrozole. The sentiments expressed by the women in that study (Wickersham et al., 2011) were consistent with the findings of the present study; however, only two of the women in the qualitative analysis (Wickersham et al., 2011) mentioned weight gain or weight loss in their descriptions of their medication-taking experiences with anastrozole. It is possible that women who had weight concerns had discontinued therapy with anastrozole before the interviews, or attributed weight concerns to another process, such as aging.

The interaction of DCIS tumor type and primary occupation is puzzling. Published reports examining similar interactions were not found. It is important to note that participants in both The AIM Study and The ONS Study with DCIS also had another tumor type to be eligible for the parent studies. While our findings suggest that women without DCIS tumor type and whose occupation was not administrative or clerical were more adherent at six-months post-treatment, further discrimination of primary occupation and tumor type and their relationships to nonadherence is needed.

The results of out study should be interpreted with several limitations in mind. The most important limitation is the cross-sectional nature of our analyses. While our findings have provided insight for future investigations of nonadherence and women with early stage breast cancer receiving hormonal therapy, no associations regarding causality can be made. All tumor types were examined as candidate predictors, but participants with DCIS also had another tumor type to be eligible for the parent studies. We chose a six-month summary statistic of nonadherence as the dependent variable, but we did not include examinations of dose intervals (the time between each dose of hormonal therapy), which may provide further information as to the patterns of the women's adherence. Furthermore, several adherence rates were extremely low (e.g. 1.52%); they were verified to be correct, but the score may have reflected a testing of the MEMS cap or one use only. It is possible pill minders were used by the women but not reported, also potentially affecting our findings.

The samples of women from The AIM and The ONS Studies examined in this analysis were uneven. While no unexpected differences between the two groups were noted at baseline, it is likely that the sample size of women selected from The ONS Study was too small to generate significant findings. We did not include lobular carcinoma in situ as a type of breast cancer in

our analyses because there was only one case in the combined sample; therefore, the results cannot be generalized to women with that type of breast cancer. Additionally, all women in our sample were white and well educated. Racial/ethnic disparities in treatment could have an effect on nonadherence and should be further investigated.

Our findings suggest future directions of inquiry with regard to nonadherence for women with early stage breast cancer who receive therapy with oral hormonal agents. First, we did not include type of surgery for breast cancer, social support, and beliefs about medicines in our analyses, all of which could provide additional insight for potential predictors of nonadherence. We used multiple linear regression analysis with a continuous nonadherence variable; other approaches could include logistic regression using 80% and/or 90% as cut-offs for adequate adherence. Future studies should also include exploration of employment and types of primary occupation and their relationship to nonadherence, as well as the effects of nonadherence on clinical outcomes and predictors of nonadherence for women with breast cancer taking oral chemotherapies or targeted therapies. Our study offers insight into potential predictors of nonadherence for women participating in one of two large cohort studies. The findings suggest additional examinations of nonadherence concerning work and symptom burden and their relationship to nonadherence are indicated.

**2.5.2.8 References**

Alfano, C. M., McGregor, B. A., Kuniyuki, A., Reeve, B. B., Bowen, D.J. … & McTiernan, A. (2006). Psychometric properties of a tool for measuring hormone-related symptoms in breast cancer survivors. *Psycho-Oncology, 15*, 985-1000.

The ATAC (Arimidex, Tamoxifen, Alone or in Combination). (2002). Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *The Lancet, 359*, 2131-2139. doi: 10.1016/S0140-6736(02)09088-8

Atkins, L. & Fallowfield, L. (2006). Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *European Journal of Cancer*, *42*(14), 22711-2276. doi: 110.1016/j.ejca/2006.03.004

Beck, A. T, Steer, R. A, & Brown, G. K. (1996). *Beck Depressive symptoms Inventory-II*. San Antonio: The Psychological Corporation.

Barron, T. I., Connolly, R., Bennett, K., Feely, J., & Kennedy, M. J. (2007). Early discontinuation of tamoxifen: A lesson for oncologists. *Cancer, 109*, 832-839. doi: 10.1002/cncr.22485

Cassileth ,B., Soloway, M.S., Vogelzang, N.J., Chou, J.M., Schellhammer, P.D. …& Kennealey, GT. (1992). Quality of life and psychosocial status in stage D prostate cancer: Zoladex Prostate Cancer Study Group. *Quality of Life Research, 1*, 323-329.

Cella, D., Land, S. R., Chang, C. -H., Day, R., Constantino, J .P. … & Ganz, P. A. (2007). Symptom measurement in the Breast Cancer Prevention Trial (BCPT) (P-1): psychometric properties of a new measure of symptoms for midlife women. *Breast Cancer Research and Treatment, 109*, 515-526.

Cramer, J. A., Scheyer, R. D., & Mattson, R. H. (1990). Compliance declines between clinic visits.[comment]. *Archives of Internal Medicine,150,*1509-1510.

Cohen J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Lawrence Erlbaum Associates.

Cohen, M. (2002). First degree relatives of breast cancer patients: Cognitive perceptions, coping, and adherence to breast self-examination. *Behavioral Medicine, 28,* 15-22.

Coombes, R. C., Hall, E., & Gibson, L. J. (2004). A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *New England Journal of Medicine, 350,* 1081-1092.

De Geest, S., Shafer-Keeler, P., Denhaerynck, K., Thannberger, N., Kofer, S. Bock, A. …& Steiger, J. (2006). Supporting medication adherence in renal transplantation in (SMART): a pilot RCT to improve adherence to immunosuppressive regimens. *Clinical Transplant, 20,* 259-368. doi: 10.1111/j.1399-0012.2006.00493.x

Demisse, S., Silliman, R. A., & Lash, T. L. (2001). Adjuvant tamoxifen: Predictors of use, side effects and discontinuation in older women. *Journal of Clinical Oncology, 19,* 322-328.

Evangelista, L. S., Doering, L. V., Dracept, K., Westlake, C., Hamilton, M., & Fonarow, G. C. (2003). Compliance behaviors of elderly patients with advanced heart failure. *Journal of Cardiovascular Nursing, 18,* 197-208.

Fink, A. K., Gurwitz, J., Rakowski, W., Guadagnoli, E., & Silliman, R. A. (2004). Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. *Journal of Clinical Oncology, 22*(16), 3309-3315. doi: 10.1200/JCO.2004.11.064

Ganz, P., Greendale, G. A., Petersen, L., Zibecchi, L., Kahn, B., & Belin, T. R. (2000). Managing menopausal symptoms in beast cancer survivors: Results of a randomized controlled trial. *Journal of the National Cancer Institute, 92,*1054-1064.

Goss, P. E., Ingle, J. N., & Martino, S. (2003). A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *New England Journal of Medicine, 349,* 1793-1802.

Grunfeld, E. A., Hunter, M. S., Sikka, P., & Mittal, S. (2005). Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Education and Counseling, 59,* 97-102. doi: 10.1016/j/pec.2004.10.005

Haynes, R., Ackloo, E., Sahota, N., McDonald, H., & Yao, X. (2008). Interventions for enhancing medication adherence (review). *The Cochrane Collaboration, 2,* 1-127.

Jonat, W., Pritchard, K. I., Sainsbury, R., & Klijn, J. G. (2006). Trends in endocrine therapy and chemotherapy for early breast cancer: A focus on the premenopausal patient. *Journal of Cancer Research and Clinical Oncology, 132,* 275-286.

Kahn, K. L., Schneider, E. C., Malin, J. L., Adams, J. L., Epstein, A. M. (2007). Patient centered experiences in breast cancer: Predicting long-term adherence to tamoxifen use. *Medical Care, 45,* 431-439.

Lash, T. L, & Fox, M. P., Westrup, J. L., Fink, A. K., & Silliman, R. A. (2006). Adherence to tamoxifen over the five-year course. *British Cancer Research and Treatment, 99,* 215-220. doi: 10.1007/s10549-006-9193-0

Lebovits, A. H., Strain, J. J., Schleifer, S. J., Tanaka, J. S., Bhardwaj, S., & Messe, M. R. (1990). Patient noncompliance with self-administered chemotherapy. *Cancer, 65,* 7-22.

Love, R. R., Cameron, L., Connell, B. L., & Leventhal, H. (1991). Symptoms associated with tamoxifen treatment in postmenopausal women. *Archives of Internal Medicine, 151*(9), 1842-1847.

Mason, B. J., Matsuyama, J. R, & Jue, S. G. (1995). Assessment of sulfonylurea adherence and metabolic control. *Diabetes Educator, 21*, 52-57.

McNair, D., Lorr, M., & Droppleman, L. F. (1992). *EdITS Manual for the Profile of Mood States*. San Diego: EdITS/Educational and Industrial Testing Service.

Newman, L. A. & Singletary, S. E. (2007). Overview of adjuvant systemic therapy in early stage breast cancer. *Surgical Clinics of North America, 87,* 499-509.

Osterberg, L. & Blaschke, T. (2005). Adherence to medication. *The New England Journal of Medicine, 353*, 487-497.

Partridge, A. H., Wang, P. S., Winer, E. P., & Avorn. J. (2003). Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *Journal of Clinical Oncology, 21*(4), 602-606. doi: 10.1200/JCO.2003.07.071

Partridge, A. H., LaFountain, A., Mayer, E., Taylor, B. S., Winer, E., & Snis-Alibozek, A. (2008). Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *Journal of Clinical Oncology, 26*(4), 556-562. doi: 10.1200/JCO.2007.11.5451

Rolley, J. X., Davidson, P. M., Dennison, C. R., Ong, A., Everett, B., & Salamonson, Y. (2008). Medication adherence self-report Instruments: Implications for practice and research. *Journal of Cardiovascular Nursing, 23*(6), 497-505.

Sedjo, R. L. & Devine, D. (2011). Predictors of non-adherence to aromatase inhibitor therapy among commercially insured women with breast cancer. *Breast Cancer Research and*

*Treatment, 125,* 191-200. doi: 10.1007s10549-010-0957-6

Spreen, O. & Strauss, E. (1998). *A Compendium of Neuropsychogical Test: Administration, Norms, and Commentary.* New York: Oxford University.

Sprinkle, S. D, Lurie, D., Insko, S. L, Atkinson, G., Jones, G. L…. & Bissada, N. N. (2002). Criterion validity, severity cut scores, and test-retest reliability of the Beck Depression Inventory-II in a university counseling center sample. *Journal of Counseling Psychology, 49,* 381-385.

Stanton, A., Bernaards, C. A., & Ganz, P. A. (2005). The BCPT Symptom Scales: A measure of physical symptoms for women diagnosed with ar at risk for breast cancer. *Journal of the National Cancer Institute, 97,* 448-456. doi: 10.1093/jnci/dji069

Stukenberg, K. W., Dura, J. R., & Kiecolt-Glaser, J. K. (1990). Depression screening scale validation in an elderly, community-dwelling population. *Psychological Assessment, 2,* 134-138.

Terhorst, L., Blair-Belansky, H., Moore, P.J., & Bender, C. (2010). Evaluation of the psychometric properties of the BCPT Symptom Checklist with a sample of breast cancer patients before and after adjuvant therapy. *Psycho-Oncology,* 20, 961-968. doi: 10.1002/pon.1806

Viele C. (2007). Managing oral chemotherapy: The healthcare practitioner's role. *American Journal of Health-System Pharmacists*, *64*(Supp 5), S25-S32.

Waterhouse, D. M., Caizone, K. A., Mele, C., & Brenner, D. E. (1993). Adherence to oral tamoxifen: A comparison of patient self-report, pill counts, and microelectronic monitoring. *Journal of Clinical Oncology, 11*(6), 1189-1197.

Wickersham, K., Happ, M. B., & Bender, C. M. (2011). Self-reported side effects and side effect severity regarding medication-taking for women with breast cancer taking oral aromatase inhibitor therapy [Abstract BU]. *Oncology Nursing Forum, 38*(1), A1-A90. doi: 10.1188/11.ONF.E60

Ziller, V., Kalder, M., Albert, U. -S., Holzhauer, W., Ziller, M…& Hadji, P. (2009). Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Annals of Oncology, 20*, 431-436. doi: 10.1093/annonc/mdn646

# 3.0 RESEARCH DESIGN AND METHODS

## 3.1 DESIGN

We explored the process of medication-taking for adults with NSCLC receiving oral EGFR inhibitor therapy. We aimed to describe the process of medication-taking and identify factors influencing medication-taking of the prescribed regimen. The philosophical orientation that informed our methods and analysis was positivist grounded theory for the purpose of constructing, testing, and refining theory from data (Corbin & Strauss, 2008; Glaser & Strauss, 1967). Medication-taking behaviors including factors or barriers influencing adherence to oral EGFR inhibitors in the target population were unknown; thus, a qualitative study to discern the perspectives of patients receiving these agents were needed to (a) organize the knowledge gained, (b) develop the appropriate theoretical basis to direct future investigations of medication-taking of oral cancer therapies, and (c) eventually, once tested, guide clinical practice (Cobb & Hagemaster, 1987; Corbin & Strauss, 2008). Qualitative inquiry has provided essential and unique information regarding medication-taking behaviors and adherence in other patient samples (Erlen & Happ, 2006; Lehane et al., 2008; Lewis et al., 2006; Russell et al., 2003). Grounded theory study designs have been used in research seeking to develop a better understanding of similar phenomena, such as adherence of persons living with HIV/AIDS to

highly active antiretroviral therapy (HAART) (Gray, 2006), the work of adherence (McCoy, 2009), and medication-taking behavior of older adult cardiac patients (Chen et al., 2007).

## 3.2 SETTING

Patients treated for NSCLC at the University of Pittsburgh Cancer Institute (UPCI) were the participants in this study. The UPCI is the only National Cancer Institute-designated Comprehensive Cancer Center in western Pennsylvania and includes over 40 locations in a radius of 200 miles around the greater Pittsburgh area. From 2008-2011, 3975 patients (1999 male [50.3%], 1976 female [49.7%]) were diagnosed with NSCLC and underwent a first course of treatment at a UPMC Cancer Center. Of those patients, most were white (88.6%), aged 60 years or older (79.5%), and diagnosed at stage III/IV (58.2%). Generally, most patients with advanced stage NSCLC who are treated at the UPCI receive therapy with an oral EGFR inhibitor at some point in their treatment trajectory.

## 3.3 SAMPLE

Based on the methodological literature and similar qualitative research reports, it was expected that 14-20 participants would be needed to achieve saturation and redundancy in the analysis and to fully address the research questions (Ledlie, 1999; Patton, 2002; Sandelowski, 1985). Theoretical saturation was achieved after 13 participants were enrolled. The University of Pittsburgh Institutional Review Board approved this study. Informed consent was obtained from

all participants prior to data collection. The sample included patients treated for NSCLC at two outpatient lung cancer clinics at a National Cancer Institute-designated cancer center. The primary investigator (PI; KW) was not part of the clinical care team and used clinic observations and chart reviews to screen eligible patients and to understand the participant's treatment trajectory. Members of the clinical team comprised of an oncologist, a nurse practitioner or physician's assistant, and a collaborative nurse identified potential participants and approached them to assess their interest in study participation. The PI met with interested patients in a private area (e.g., conference room, clinic exam room) or discussed by phone detailed information about the study's requirements.

### 3.3.1 Inclusion criteria

Men and women over 18 years of age with NSCLC (any type/stage) receiving an oral EGFR inhibitor and able to speak, read, and understand the English language (since all interviews were conducted in English) were eligible to participate. Although patients with NSCLC are typically older than 65 years of age, patients 20 years of age and older with NSCLC have been treated at UPCI. Oral EGFR inhibitors are currently approved for 2nd and 3rd line treatment of advanced stage NSCLC adenocarcinomas and are recommended as 1st line treatment for patients with NSCLC and EGFR mutation. However, the disease type and stage of patients with NSCLC enrolled in clinical trials may vary; therefore, patients with any type and any stage of NSCLC receiving oral EGFR inhibitors were eligible for the study. Verification of NSCLC diagnosis was confirmed by the oncologist and identified using medical record review.

### 3.3.2 Exclusion criteria

Exclusion criteria included a primary cancer that had metastasized to the lung or a second primary cancer, current metastasis to the central nervous system, or evidence of cognitive impairment as assessed by the Mini-Mental Status Exam (MMSE) (Folstein, Folstein, & McHugh, 1975). Patients with treated brain metastases may still have had evidence of these on repeat imaging, although the brain metastases may be stable or have regressed, which is adequate response to treatment. The majority of patients with NSCLC are diagnosed over the age of 65 and the central nervous system is a common site for metastases (NCCN, 2011). Because disease-related oxygenation issues and age-related cognitive impairment may affect medication-taking behavior, participants were screened for cognitive impairment at baseline with the MMSE, an 11-item screening test that includes an evaluation of higher level verbal and nonverbal functioning (Folstein et al., 1975). Age and level of education have been associated with cognitive function; therefore, eligibility was determined based on age and education scaled normative data when using the MMSE. Potential participants who scored are at or below the borderline range (1.4 standard deviations below the norm) were excluded (Folstein et al., 1975; Spreen & Strauss, 1998).

### 3.3.3 Sampling procedure

Participants were purposively selected for variation in gender, race/ethnicity, age and time in therapy (Sandelowski, Holditch-Davis, & Glenn Harris, 1989). Purposive sampling also included those who underwent reductions in dose of their EGFR inhibitor and those who discontinued therapy (e.g., due to disease progression), because dose reductions and therapy discontinuation

are important variations (and perhaps consequences) of their medication-taking process. Four participants were well established in their therapy (e.g., taking for approximately 1 year) and nine were either in an early phase of treatment (e.g., first week to two months into treatment) or their medication-taking process changed during the course of the study (e.g., discontinued therapy due to disease progression). Research and clinical experiences show that EGFR inhibition-related rash commonly occurs during the first one to three weeks of treatment, although the time to rash appearance may be related to the agent and dose (Kris et al., 2003; Sipples, 2006). Additionally, EGFR-inhibition associated diarrhea is experienced by approximately 75% of patients taking erlotinib (Sipples, 2006). Therefore, participants at various points in their treatment trajectory were enrolled in the study to understand how targeted pathway-specific side effects may affect medication-taking. Theoretical sampling focused on age and type of health insurance coverage.

### 3.3.4 Enrollment procedure

After approval of the protocol by the UPCI Protocol Review Committee and the University of Pittsburgh Institutional Review Board (IRB), participants at a National Cancer Institute (NCI)-designated cancer center were invited to enroll. Prior to the start of the study, the principal investigator (PI) met with the oncologists, the nurse practitioner, the physician's assistant and the collaborative nurses at two lung cancer clinics at the cancer center to discuss the study, including eligibility criteria. Recruitment occurred in one of two ways:

1. The oncologists, nurse practitioner, physician's assistant, or collaborative nurses identified patients receiving therapy with oral EGFR inhibitors either through their daily practice or through review of a Health Insurance Portability and Accountability Act

(HIPPA) compliant database. Once identified, the oncologist, the nurse practitioner or physician's assistant, or the collaborative nurse approached patients to assess interest in study participation.

2. IRB approved study advertisements were posted in the clinic waiting areas of UPCI (Appendix). The flyers directed interested potential participants to call the investigator for additional information concerning the study.

### 3.3.5 Procedures for data collection

After a member of the clinical team introduced the investigator to potential participants expressing an interest in learning more about the study, the PI either met with the patient in a private area (i.e., conference room, clinic exam room) or discussed by phone detailed information about the study's purpose and requirements to determine the patient's interest and/or responded to any questions participants may ask about the study. If willing to participate, patients were asked to sign an IRB-approved consent form that explained the study and its risks and benefits, and enrollment procedures commenced. Informed consent was obtained prior to the performance of any study procedures. Participants were informed that their desire to participate in the study would under no circumstances affect their care and treatment at the UPCI or UPMC Cancer Centers or their eligibility to participate in any other clinical trial. They were also informed that their data would be reported as a group. If the participant's spouse or significant other wished to participate, the PI made it clear that the research concerned the participant's responses and not the effect that their cancer may have had on loved ones or family members. If the participant or spouse/significant other insisted that the spouse/significant other be present for the interview, and the spouse/significant other's volunteered information about the participant's

medication-taking experiences, the information was viewed as a "data source" and not as a participant, and their information was retained in the interview transcript for analysis.

Once participants were enrolled, data collection (Table 7) began in a private conference room at the UPCI or a private area in the participant's home. If none of these locations were convenient for the participant, the interview was held at a location preferred by the participant that afforded privacy and convenience.

**Table 7: Summary of data collection procedures**

| | **Screening** | **Baseline** | **Initial Interview** | **Follow-Up Interviews** |
|---|---|---|---|---|
| NSCLC diagnosis / Oral targeted therapy | X (By health care provider.) | X | | |
| Informed Consent | | X (Before any research procedures.) | | |
| Mini Mental Status Exam (MMSE) | | X | | |
| Demographics | | X | | |
| Prior Chemotherapy / Radiation Therapy / Other treatment | | X | | |
| Confirmation of Eligibility<br>1. Confirmation of diagnosis/oral targeted therapy<br>2. MMSE | | X | | |
| Interviews | | | X | X (For patients enrolled in an early phase of their treatment.) |

Note. NSCLC = non-small cell lung cancer.

#### 3.3.5.1 Baseline procedures

***Sociodemographic information*** After informed consent, participant age, race/ethnicity, insurance coverage, religion, occupation, marital status, and level of education were recorded at the baseline visit using a sociodemographic case report form developed for this study (Appendix).

***Prior chemotherapy, radiation therapy, and/or other treatment for NSCLC*** Prior NSCLC treatment information including chemotherapy and radiation therapy (i.e. dose, timing) was extracted from the participant's medical record and recorded on a case report form developed for this study (Appendix). In addition, the reason for discontinuation or dose reduction of oral targeted therapy was extracted from the medical records, where such changes are documented. EGFR mutation status was recorded; patients at the cancer center are told of their status, and are aware that as such they may respond better to their treatment.

***Assessing for cognitive impairment*** Participants were assessed for cognitive impairment through the use of the MMSE. Level of cognitive ability needed for any research study depends on the tasks required of the participant. "Most studies report that the MMSE is sensitive to the presence of dementia, particularly in those with moderate to severe forms of cognitive impairment. The test, however, is less than ideal when those with mild cognitive impairment are evaluated..." (Spreen & Strauss, 1998, p. 66). Participants in this study were required only to participate in interviews; mild forms of cognitive impairment should not preclude that participation. Because age and level of education are associated with cognitive function, eligibility was determined based on age and education scaled normative data. Potential participants whose scores were at or below the borderline range (1.4 standard deviations below the norm) were to be excluded.

Administration time for the MMSE is 5 minutes. Test-retest reliability of the MMSE, 24 hours apart, is interpreted as $r$ =. 88. Concurrent validity with the verbal intelligence quotient (IQ) of the Wechsler Audit Intelligence Scale in 137 psychiatric and healthy patients is interpreted as $r$ = .77 ($p$ < .0001) and with the performance IQ is r = .66 ($p$ < .001) (Folstein et al., 1975).

***Confirmation of eligibility*** The oncologist verified the participant's diagnosis of NSCLC. MMSE data were scored, interpreted, and reviewed with a faculty member with expertise in this area (Dr. C. Stilley, Neuropsychology Consultant). Once eligibility was confirmed, an interview was scheduled.

## 3.4 INITIAL AND FOLLOW-UP INTERVIEWS

Interviews were the primary data source for this study. We interviewed most participants ($n$ = 10) on multiple occasions over nine months to capture the medication-taking process in early, middle and later phases of medication use. In-depth semi-formal ($n$ = 27) and brief ($n$ = 5) interviews were conducted with 13 participants (1153 pages of data). Four participants were well established in their therapy (e.g., taking for approximately 1 year) and nine were either in an early phase of treatment (e.g., first week to two months into treatment) or their medication-taking process changed during the course of the study (e.g., discontinued therapy due to disease progression). The PI conducted digitally-recorded interviews ranging from 32 to 90 minutes from August 2011 to July 2012 either at the participant's home or at a location convenient for the participant (e.g., private space at the cancer center, coffee shop) (Erlen & Happ, 2006; Lewis et al., 2006; Wickersham et al., 2011). The interview guide consisted of questions about oral EGFR

inhibitor medication-taking behaviors (Appendix). Brief telephone interviews were conducted for further validation or exploration of themes identified during data analyses. When a spouse or family support person was present during the interview (at patient's request/agreement), their contributions were included in the transcript for analysis. The recorders failed for one interview, which was reconstructed immediately. Participants received $10 for each interview.

Supplemental data sources included an erlotinib starter kit, journals/newsletters, prescription inserts, and personal documents (e.g., transcript of a speech) given to the PI by the participants or the clinical team. The ongoing analysis generated additional interview questions about treatment delays, usefulness of support groups for patients receiving oral EGFR inhibitors, prescription medication insurance coverage, and disclosure of lung cancer and/or EGFR inhibitor use to family or friends.

### 3.4.1 Interview procedure

An interview checklist was used to organize activities related to the interview (Appendix). Once an interview was scheduled, the participant study number and interview date were recorded on a tracking spreadsheet. One day before the interview, the PI called to confirm the interview and printed: two informed consent forms (one for signature to bring back and file and one for the participant), the interview guide and observational notes, and the participant payment form. At the time of the phone call, the PI confirmed the date, time, and convenience and privacy of the location with the participant. For the majority of the participants (12/13) the interview occurred on the same day the assessment procedures were completed for their convenience. On the day of the interview, the PI brought a digital tape recorder with a back-up recorder and batteries, directions to the interview location, informed consent forms, MMSE, sociodemographic case

report form, and participant stipend. After the informed consent process, MMSE administration, and confirmation of eligibility, the interview commenced Particular effort was made to place the subject at ease; a broad, grand tour question (Appendix) was used to gently open the conversation: "Tell me what it is like for you to take that medication." Questions about their medication-taking related to oral EGFR inhibitor use included how they took their EGFR inhibitor on a typical day and missing or skipping doses of their medication. Immediately after the interview, the PI checked the tape recorder to ensure the interview had been recorded, and to record impressions of the interview. Within 24 hours of the interview, the PI downloaded the interview, transferred it and the transcript template to the digital Dropbox, and entered the completion of interview onto the tracking sheet. The PI then emailed the transcriptionist to notify her that an audio-file was ready for transcription.

## 3.5 DATA ANALYSES

During analysis, emerging findings generated additions to the interview guide; new questions addressed delay in treatment, the usefulness of support groups for patients with lung cancer receiving oral targeted therapy, and disclosure of oral targeted therapy to family or friends. These concepts were explored in subsequent interviews with new participants, as well as with select participants who had already been interviewed. Analyses to characterize the study sample included descriptive statistics, including frequencies and percentages for categorical descriptors and means, medians, standard deviations and ranges for continuous-type patient descriptors for data concerning sociodemographic information and cognitive impairment screening, and median,

mode for categorical data including NSCLC diagnosis (type and stage), EGFR mutation status, and prior and current cancer therapy.

Interviews were digitally recorded, with a back-up digital recorder and batteries available. To ensure the patient's confidentiality, each participant was assigned a unique study identification number. To safeguard participant privacy, observational notes were kept in a locked drawer and will be kept for up to six years. A separate, encrypted document linking the study identification number to participant name was kept separately in a password-protected file. All electronic files were encrypted for participant protection.

We reviewed each transcript while listening to the audio-recording for accuracy and to gain an overall impression of the participant's focus. In a cyclical fashion, the transcribed data were examined line by line to label (open code) text that related to participants' medication-taking of oral EGFR inhibitor therapy. Similar codes were grouped into categories. We then examined the relationships between categories of codes (axial coding) among the participants. Selective coding was used to identify and systematically connect the core category with other categories (Corbin & Strauss, 2008). ATLAS.ti (6.2.27) (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) software was used for data management.

Other analysis techniques included (Corbin & Strauss, 2008) questioning the data, thinking "outside of the box," and developing provisional answers to become familiar with the data. Dimensional analysis was used to examine variations of a concept that give specificity and range to a concept (Schatzman, 1990). For example, the positive and negative experiences that patients encountered with their health care professionals were dimensionalized in tabular form. Additionally, dimensions and exemplars of prescription co-payment requirements (i.e., one co-pay for each strength of erlotinib) and assistance programs utilized by the participants were also

examined in tabular form. We used matrix construction for comparison and pattern recognition (Miles & Huberman, 1994). Matrices were developed for side effect severity and for the comparison of the fifth and sixth participants, who were key informants but who had different health care professional experiences, issues with the cost of erlotinib, type of health care insurance, side effects and side effect severity, aging, and "death talk." Three matrices were constructed for the purpose of comparing and contrasting all thirteen participants with the major themes we discerned from the data. Writing the story was especially important as more than one story was possible from the data. Case titles and story summaries were developed for each participant, as well as for the group to help identify the basic psychosocial process. Finally, the literature was used to make comparisons, stimulate analytic questions, confirm findings or show where our findings differ from the literature, or where the current literature only partially explains the medication-taking process for patients with NSCLC receiving therapy with oral EGFR inhibitors (Strauss & Corbin, 2008).

Sampling, interviewing, and analysis continued until we reached informational redundancy (i.e., no new themes or patterns were recognized; $n = 8$); we then enrolled three participants for further sample diversity and to confirm existing findings. One woman was selected for type of health insurance carrier, because health insurance and cost of erlotinib were major concerns expressed by the participants. One man was selected for younger age. No new themes emerged; we achieved theoretical saturation after 13 participants were enrolled.

### 3.5.1 Training

The researcher completed initial ATLAS.ti training in July 2008. Qualitative interviewing skills and ATLAS.ti data management were reinforced through preliminary work with her NRSA Co-

Sponsor (Dr. C. Bender) and Qualitative Methods Co-Investigator (Dr. M.B. Happ) (Preliminary Work) and independent studies (Advanced Qualitative Analysis) for implementation of research concepts and methods appropriate for the current study. A student worker transcribed interview data for the AIM nested companion study (Preliminary Work) and underwent transcription training at that time. The same person transcribed interview data for the current study.

### 3.5.2 Trustworthiness

To ensure rigor of this qualitative study, the following steps were implemented to assure the trustworthiness of the data, analysis, and research process.

#### 3.5.2.1 Credibility

A faculty researcher (MBH) with experience in grounded theory audited all coding to ensure the credibility of the data analysis. Weekly analysis meetings were conducted with the faculty researcher and a qualitative work group to review and discuss data exemplars, coding, theoretical insights, and analytic decisions. Extensive member checking was conducted by use of several methods. Three key informants were selected to review and comment on the constructed theory to confirm or refine the interpretive analysis. The informants were well-educated and invested in the project; one asked to see her specific quotations that would be used in the final study summary. Thus, we provided a summary of the findings in lay language with quotations to the informants for their review. All three confirmed the conceptual model. We reviewed public websites (e.g., Cancer Grace and Inspire) demonstrated that patients with advanced stage NSCLC have similar concerns about treatment for lung cancer and management of side effects and provided external validation of the psychosocial process. We reviewed and coded a publicly

available interview transcript of a personal interest story. Findings were shared with the clinical team, who confirmed the difficulty that patients encounter in paying for erlotinib and with managing side effect severity. Findings were also shared with the infusion nursing staff of the second floor treatment center of the UPCI, who confirmed the study results.

#### 3.5.2.2 Confirmibility and dependability

All interview data, field notes, and memos were documented to provide an audit trail. Methodological memos were used to document operational decisions, timing, or sequencing of data collection and participant selection (Corbin & Strauss, 2008). Theoretical memos were used to show the development of insights, dimensions of the process, and analytic decisions. All memos were recorded in Atlas.ti, dated, titled, and cross-referenced to provide a complete audit trail of the inductive logic of the PI and analytic team.

## 3.6 PARTICIPANTS

### 3.6.1 Research participant risk and protection

Efforts were undertaken to minimize the risk to confidentiality of data and to anonymity of the participants. All participants were assigned a unique code number under which all data were stored. Security of the data was upheld through the use of password protection and restricted access to users. Consent forms and a list of the match between participant names and code numbers were retained in separate locked drawers of the PI's desk, which is also in a locked room, providing further security.

This was a minimal risk study; however, during the interview process, participants could experience emotional distress or fatigue.

#### 3.6.1.1 Emotional distress

Formal interview training was completed. During this training, the researcher had the opportunity to learn how best to assess for potential emotional distresses during the interview as this distress occurs on a continuum. Each participant was instructed that s/he could choose not to answer any question that caused uneasiness. Several participants became tearful during their interview; however, the researcher immediately addressed it and confirmed with the participant his/her willingness to continue. The plan established prior to the start of the study was as follows: should a participant express any emotional discomfort, the researcher would immediately address it. If not acute, such as a side effect not previously reported or discomfort felt as a result of the interview was brought to her attention the researcher would negotiate with the patient to report the problem him- or herself to the oncologist or primary care provider. The researcher would also offer to make this phone call, if needed. If the problem was acute, meaning the participant felt the need to stop the interview, the researcher would immediately offer to stop the interview and resume it at a later date. If participants became distressed while completing the interview and were in need of psychological counseling or psychiatric referral, appropriate referral information would be provided (Appendix). The informed consent form (Appendix) provided additional detail about the process for addressing emotional distress.

#### 3.6.1.2 Fatigue

To minimize fatigue, participants were offered breaks during the interview. Participants were instructed during the informed consent process that they could choose to discontinue the interview at any time for any reason, if needed. All potential discomforts and procedures to alleviate discomfort were discussed with the participants and were delineated clearly in the informed consent document. Participants did not directly benefit from participating in this study. However, they were helping to extend the knowledge of the process of medication-taking in patients with NSCLC taking oral targeted therapies, providing a basis for future work in developing an intervention to enhance medication-taking to be tested in future research.

#### 3.6.1.3 Risk of breach of confidentiality

There was a possibility of the risk of breach of confidentiality of protected health information. The researcher took all necessary steps to ensure that this did not happen. All records related to the participant's involvement in this research study were stored in a locked file cabinet. Their identity on these records were indicated by a case number rather than by their name, and the information linking these case numbers with their identity were kept separate from the research records. They were informed that they would not be identified by name in any publication of the research results unless they signed a separate consent form giving their permission (release).

Photographing objects related to the participant's medication-taking process did not impose additional risks; the researcher ensured that there was nothing in the image of the object that would identify the participants, or that would identify the participants as a patient with non-small cell lung cancer, or any cancer. The photographs of the objects taken during their interviews were for the purpose of recording and describing this project. These images may appear in academic publications, presentations given at academic conferences, or on the Internet.

These photographs may also appear in newspapers or newsletters. The participants were informed that they could participate in the research study, without being recorded, even if they did not sign this form.

As the study was not a clinical trial, the PI was responsible for the ongoing evaluation of the progress of the study and was guided by the dissertation committee. Data safety and monitoring meetings were conducted on a bi-monthly basis to review study conduct, recruitment, accrual, confidentiality issues, and results and to make changes as needed.

### 3.6.2 Participant characteristics

This study enrolled both men and women with NSCLC. No participant was excluded based on race or ethnicity. In 2010, the composition of Allegheny county was 13.2% African American, 1.6% Hispanic or Latino, and 2.8% Asian (US Census Bureau, 2012a). In 2010, the composition of the city of Pittsburgh was 26.1% African American, 2.3% Hispanic or Latino, and 4.4% Asian (US Census Bureau, 2012b). At the UPCI, from 2008-2011 patients with NSCLC were predominantly white (87.0%). These statistics differ from both those of the city of Pittsburgh and of patients with NSCLC nationally; the expectation was that at least 18% of the eligible sample for this study would be a minority, predominately black. In the participant sample, 15% of the participants were a minority.

Although patients as young as 20 year of age with NSCLC have been treated at UPCI, no children were enrolled in this study. The study primarily focused on an older adult population, as this is the group that is most likely to be affected by NSCLC. In this participant sample, participants' ages ranged from 52 to 83 years of age.

## 4.0 SUMMARY OF STUDY

The purpose of this study was to explore the process of medication-taking for adult patients with NSCLC receiving oral EGFR inhibitor therapies. Specifically, we aimed to (a) describe the process of medication-taking, and (b) identify factors influencing medication-taking regarding their prescribed regimen. Three manuscripts were developed in support of this project. The first is an account of our preliminary work that was submitted to *Nursing Research and Practice* on June 11, 2012. The second is a report of a secondary analysis that examined pre-treatment patient-, illness-, and treatment-related predictors of adherence to oral hormonal therapy for women with early stage breast cancer. This report is in draft form and will be finalized after dissertation defense. It is formatted for *Nursing Research*. The third manuscript is a report of the main findings from the dissertation research, which has been formatted for submission to *Social Science and Medicine*.

## 4.1 ISSUES

Originally, enrollment was to occur through one of two ways: by members of the clinical team and through the use of an IRB approved study advertisements. The advertisement was posted on the bulletin board of the UPCI 2$^{nd}$ floor treatment waiting area (Appendix); however, no participants were identified through this method. Initially, if needed, additional sites in the

UPMC Cancer Center system were to be added to improve enrollment. Ultimately, three additional oncologists and a second lung cancer clinic at the UPCI were added to improve recruitment; however, it was not necessary to add additional external sites.

Although the PI was not part of the clinical team, she spent time in the lung cancer clinic as part of the BSN to PhD clinical exposure and training (oncology content) and to recruit participants directly from the clinic setting. The clinical training and observation did at times inform understanding and analysis. Memos were recorded in Atlas.ti about recruitment and chart review, which helped the PI understand the patients' treatment trajectory and to identify patients.

## 4.2 METHODS

Following grounded theory methodology, emerging findings generated changes to the interview guide, including questions about delays in treatment, usefulness of support groups for patients with NSCLC receiving oral EGFR inhibitor therapy, and disclosure of lung cancer and/or oral EGFR inhibitor use to family or friends. These concepts were explored in subsequent interviews with new participants as well as with select participants who had already been interviewed.

During the interviews, if the participant's family support person wished to participate, the PI made it clear that the research concerned the participant's responses and not the effect that their cancer may have had on loved ones or family members. If the participant or family support person insisted that he/she be present for the interview, and that person volunteered information about the participant's medication-taking experiences, the information was viewed as a "data source" and not as a participant, and their information was retained in the interview transcript for analysis. Several of the participants wished to have their spouse or family support person present

during the interview. Generally, these interviews went well, and in many cases, the support person provided key information concerning the participant's medication-taking process. In one instance (third interview of 1003), the support person was unintentionally disruptive, requiring the PI to continuously refocus the interview to the participant. This single instance was documented in Atlas.ti.

During an analysis meeting in February 2012, the dissertation committee recognized that many participants mentioned artifacts that were important to them for their medication-taking process. Artifacts were defined as products that held meaning about the culture of the user (Tilley, 2000). For this study, artifacts related to medication-taking may have included a medication diary or notebook and storage containers. The dissertation committee agreed that photographs of these objects related to participant medication-taking were important in helping us to understand and to interpret the total process of how participants take their oral targeted therapy in the context of the participants' culture (Tilley, 2000). Additionally, consistent with grounded theory methodology, analysis of these objects helped the researcher to determine the symbolic meaning of these objects for individual participants (Cutliffe, 2000). The choice of the object to photograph was co-constructed between the research participant and the PI. Participant's personal objects were photographed, but not the participants themselves.

The original plan was for the PI to re-contact by phone participants who had already completed the interview procedures for their interest in allowing the study team to photograph their artifacts related to medication-taking. If interested, participants were to be re-consented with an informed consent addendum for their permission. Future participants were to be asked for their voluntary permission to photograph similar objects during the informed consent process. The use of artifacts was not approved by the IRB until enrollment was almost completed (April

2012). The PI approached one participant, who agreed, but the photograph of her pill container was not of adequate quality. Nonetheless, the PI did receive unsolicited artifacts (Tilley, 2000; Cutliffe, 2000) provided by the participants and the clinical team. These included an erlotinib starter kit that is distributed by the pharmaceutical company, several journals and newsletters related to cancer treatment, patient prescription inserts, and personal documents such as a speech prepared by one of the participants. The supplemental data were included with the analysis.

# 5.0 RESULTS—SURVIVING LUNG CANCER: MEDICATION-TAKING AND ORAL TARGETED THERAPY

## *5.1* COVER LETTER TO *Social Science and Medicine*

September 25, 2012

Ellen Annandale
Department of Sociology
University of Leicester
University Road
Leicester, LE1 7RH, UK

Dear Dr. Annandale:

We are submitting a manuscript entitled "Surviving lung cancer: Medication-taking and oral targeted therapy" for review and possible publication in *Social Science and Medicine.* The paper discusses the methods and findings for a qualitative study examining the medication-taking experiences for men and women with advanced stage non-small cell lung cancer receiving therapy with an oral epidermal growth factor receptor inhibitor. This manuscript has been reviewed and approved by all authors. The paper has not been submitted to any other journal; this work has not been published elsewhere.

Thank you for your consideration. If you need further information, please contact me by mail, telephone or e-mail at:

Karen Wickersham, PhD, RN
University of Pittsburgh
School of Nursing
415 Victoria Building
Pittsburgh, PA 15261
Telephone: 412-721-5899
e-mail: kew44@pitt.edu

Sincerely,

Karen E. Wickersham, PhD, RN
Doctoral Candidate
University of Pittsburgh
School of Nursing

## 5.2 ACKNOWLEDGEMENTS

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## 5.3 RESEARCH HIGHLIGHTS

- Medication-taking with an epidermal growth factor receptor inhibitor was a vehicle for surviving lung cancer.
- The participants framed Surviving Lung Cancer within the recognition of NSCLC as a life-limiting illness without cure.
- Paying for treatment, cherishing family time, and living life to the fullest were key components of surviving lung cancer.
- Access to affordable care and medication over time is crucial because insurance benefits can change or reach limits.
- Support groups addressing concerns of survivorship are needed for persons with NSCLC and their caregivers.

## 5.4 ABSTRACT

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors increase survival and improve quality of life for patients with non-small cell lung cancer (NSCLC). Because oral EGFR inhibitors are a new therapy, the implications for medication-taking are unknown. We used grounded theory to explore the process of medication-taking for patients with NSCLC who were receiving therapy with oral EGFR inhibitors. We sought to describe the medication-taking process, and identify factors influencing medication-taking. We enrolled men and women from a National Cancer Institute-designated cancer center aged 18 years or older with NSCLC receiving oral EGFR inhibitors who were able to speak, read, and understand English. Exclusion criteria

included central nervous system metastases and evidence of cognitive impairment as assessed by the Mini-Mental Status Exam. Thirteen participants were purposively selected for variation in gender (5 men/8 women), race/ethnicity (2 non-whites), age (52-83 years), time in therapy (1 week to 6 or more years), dose reductions ($n$ = 5), and therapy discontinuation ($n$ = 2). Theoretical sampling focused on age and health insurance carrier. Data were collected through 32 semiformal and brief interviews concerning one's medication-taking behaviors related to therapy with oral EGFR inhibitors. We employed constant comparative and dimensional analyses. The basic psychosocial process, *Surviving Lung Cancer*, which participants framed within the recognition of NSCLC as a life-limiting illness without cure, included a dynamic process of (a) *Deciding* to take targeted therapy with erlotinib, (b) *Preparing* for erlotinib, and (c) *Treating* lung cancer as a chronic condition. Participants described thresholds that may result in stopping erlotinib, including side effects and cost. Men described taking erlotinib therapy in partnership with their spouse; most women managed erlotinib alone. These findings may provide the theoretical basis for developing patient-centered interventions to address medication-taking.

## 5.5 INTRODUCTION

Lung cancer is the leading cause of cancer deaths in the US for both men and women, with approximately 160,340 deaths estimated for 2012 (Siegel et al., 2012). The 5-year relative survival rate for patients of all stages is 16% (Siegel et al., 2012). Traditionally, patients with non-small cell lung cancer (NSCLC) have been treated with surgery, radiation therapy, and/or intravenous chemotherapy. Recently, NSCLC treatment has shifted to the use of oral targeted therapies, such as tyrosine kinase inhibitors (Aisner, 2007). For patients with NSCLC, clinical

development of tyrosine kinase inhibitors has focused on the epidermal growth factor receptor (EGFR) with some agents already approved for clinical use. Erlotinib (Tarceva®, OSI Pharmaceuticals, Farmingdale, NY), an oral EGFR inhibitor, has been shown to increase survival, decrease symptoms, and improve physical functioning and quality of life for NSCLC patients (Bezjak et al., 2006). Furthermore, research has shown that patients with EGFR mutations, specifically deletions of exon 19 and exon 21, respond well to therapy with EGFR tyrosine kinase inhibitors (Miller et al., 2008; Sequist et al. 2008). As such, the National Comprehensive Cancer Network (2011) recommends treatment with erlotinib as first-line therapy for patients with NSCLC with an EGFR mutation.

Oral EGFR inhibitors play a key role in the management of advanced stage NSCLC. Targeted therapy for NSCLC treatment is unique in its mechanism of action and side effect profile and is generally taken daily until disease progression (weeks to years), unlike oral chemotherapy (e.g., capecitabine) or hormonal therapy (e.g., anastrozole). Medication-taking requires activities such as identifying and counting pills, timing pill taking, and refilling medication prescriptions (Russell et al., 2003). Qualitative inquiry provides unique information about medication-taking behaviors and experiences of patients with chronic disorders (Chen et al., 2007; Erlen & Happ, 2006; McCoy, 2009; Russell et al., 2003). Most qualitative studies of medication-taking of patients with cancer, however, have focused on children or adolescents who have developmental issues such as egocentrism, concrete thinking, and parental involvement (Landier et al., 2011; Malbasa et al., 2007). The medication-taking process for individuals with NSCLC taking oral EGFR inhibitors has not been described and is crucial to providing comprehensive patient-centered care and developing and testing interventions tailored to the needs of individuals with NSCLC.

## 5.6 METHODS

We explored the process of medication-taking for adults with NSCLC receiving oral EGFR inhibitor therapy. We aimed to describe the process of medication-taking and identify factors influencing medication-taking of the prescribed regimen. The philosophical orientation that informed our methods and analysis was positivist grounded theory for the purpose of constructing, testing, and refining theory from data (Corbin & Strauss, 2008; Glaser & Strauss, 1967).

### 5.6.1 Setting and Sample

The University of Pittsburgh Institutional Review Board approved this study. Informed consent was obtained from all participants prior to data collection. The sample included patients treated for NSCLC at two outpatient lung cancer clinics at a National Cancer Institute-designated cancer center in the USA. The primary investigator (PI; KW) was not part of the clinical care team and used clinic observations and chart reviews to screen eligible patients and to understand the participant's treatment trajectory. Members of the clinical team, an oncologist, a nurse practitioner, physician's assistant, or a collaborative nurse, identified and approached potential participants to assess their interest in study participation. The PI met with interested patients in a private area at the recruitment sites or discussed the study by phone.

### 5.6.2 Participants

Men and women over 18 years of age with NSCLC (any type/stage) receiving an oral EGFR inhibitor and able to speak, read, and understand English were eligible to participate. Exclusion criteria included a primary cancer that had metastasized to the lung or a second primary cancer, current metastasis to the central nervous system, or evidence of cognitive impairment as assessed by Mini-Mental Status Exam (MMSE) (Folstein et al., 1975) scores at or below the borderline range (1.4 standard deviations below the age and education scaled norm (Spreen & Strauss, 1998).

Participants were purposively selected for variation in gender, race/ethnicity, age, time in therapy, reductions in dose of their EGFR inhibitor, and discontinuation of therapy (Sandelowski et al., 1989). Theoretical sampling focused on age and type of health insurance coverage. Twenty patients were approached for their interest in the study; one was excluded for a second primary cancer and six did not enroll (e.g., unreturned calls, “too much going on,” disclosure concerns, declining performance status). The characteristics of the study participants were similar to those who did not enroll (data not reported). We achieved theoretical saturation after 13 participants were interviewed. The study sample ($N$ = 13) consisted of five men (38.5%) and eight women (61.5%) ranging from 52 to 83 years of age (Table 8).

**Table 8: Participant sociodemographic-, illness-, and treatment-related characteristics**

| Characteristic | Participants (*N* = 13) |
|---|---|
| Age (in years) | |
| *Mean (range)* | 70.5 (52 - 83) |
| Years of education | |
| *Mean (range)* | 14.6 (11 - 22) |
| Marital status *n (%)* | |
| Married | 9 (69.2) |
| Never married | 1 (7.7) |
| Widowed | 3 (23.1) |
| Ethnicity *n (%)* | |
| White | 11 (84.6) |
| African American | 1 (7.7) |
| Asian | 1 (7.7) |
| Gender *n (%)* | |
| Male | 5 (38.5) |
| Female | 8 (61.5) |
| Health care insurance coverage *n (%)* | |
| Managed Medicare | 8 (61.5) |
| Commercial Insurance | 4 (30.8) |
| COBRA | 1 (7.7) |
| Stage at diagnosis *n (%)* | |
| II/IIa | 2 (15.4) |
| IIIb/IV | 11 (84.6) |
| Reductions in dose of EGFR inhibitor therapy | 5 (38.5) |
| Discontinued therapy with EGFR inhibitor | 2 (15.4) |

Note: COBRA = Consolidated Omnibus Budget Reconciliation Act health insurance; EGFR = epidermal growth factor receptor inhibitor.

Most were retired (76.9%), white (84.6%), married (69.2%), had NSCLC adenocarcinoma (76.9%), and had managed Medicare health insurance (61.5%). Six (46.2%) had a documented mutation of the EGFR gene. Participants took erlotinib for 1 week to 6 or more years. Two participants took erlotinib as part of a clinical trial but received it through their health insurance. Three participants died during the study period. No participants were excluded due to

cognitive dysfunction. One woman declined further involvement after the first interview due to fatigue and “seeing too many doctors.”

### 5.6.3 Interviews

We interviewed most participants ($n$ = 10) on multiple occasions over eleven months to capture the medication-taking process in early, middle and later phases of medication use. In-depth semi-formal ($n$ = 27) and brief ($n$ = 5) interviews were conducted with 13 participants (1153 pages of data). Four participants were well established in their therapy (e.g., taking for approximately 1 year) and nine were either in an early phase of treatment (e.g., first week to two months into treatment) or their medication-taking process changed during the course of the study (e.g., discontinued therapy due to disease progression). The PI conducted digitally-recorded interviews ranging from 32 to 90 minutes from August 2011 to July 2012 either at the participant’s home or at a location convenient for the participant that afforded privacy (Erlen & Happ, 2006; Lewis et al., 2006; Wickersham et al., 2011). The interview guide consisted of questions about oral EGFR inhibitor medication-taking behaviors (Table 9).

**Table 9: Sample interview guide**

| Grand Tour Question | Probes |
|---|---|
| What is it like for you to take that medication? | • Why/when/how did you start?<br>• How does it make you feel?<br>• What were you told?<br>• How is it different from previous treatment? |
| Tell me how you take erlotinib on a typical day. | • What kind of strategies do you use to help you?<br>• How do you decide when to take them? |
| What do you find difficult? | • What would be your "deal breaker"? |
| Patients sometimes miss doses or find it difficult to take at the same time each day. How is that for you? | • What happens when you miss a dose?<br>• What happens when a dose is late? |
| Some people don't realize that they forget doses. Does that ever happen for you? | • Were there unexpected, non-routine things?<br>• What were you told to do if you missed a dose? |
| Do you experience any side effects that interfere with taking your medicine? | • How do you manage them? |
| Who is helpful to you in taking erlotinib? | • In what ways does he/she help?<br>• How have health care providers helped you? |

Brief telephone interviews were conducted for further validation or exploration of themes identified during data analyses. When a spouse or family support person was present during the interview (at patient's request/agreement), their contributions were included in the transcript for analysis. The recorders failed for one interview, which was reconstructed immediately. Participants received $10 for each interview.

Supplemental data sources included an erlotinib starter kit, journals/newsletters, prescription inserts, and personal documents (e.g., transcript of a speech) given to the PI by the participants or the clinical team. The ongoing analysis generated additional interview questions about treatment delays, usefulness of support groups for patients receiving oral EGFR inhibitors, prescription medication insurance coverage, and disclosure of lung cancer and/or EGFR inhibitor use to family or friends.

### 5.6.4 Data analysis

We used descriptive statistics to characterize the sample. We reviewed each transcript while listening to the audio-recording for accuracy and to gain an overall impression of the participant's focus. In a cyclical fashion, the transcribed data were examined line by line to label (open code) text that related to participants' medication-taking of oral EGFR inhibitor therapy. Similar codes were grouped into categories. We then examined the relationships between categories of codes (axial coding) among the participants. Selective coding was used to identify and systematically connect the core category with other categories (Corbin & Strauss, 2008). ATLAS.ti (6.2.27) (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) software was used for data management. Other analytic techniques included questioning the data (Corbin & Strauss, 2008), dimensional analysis (Schatzman, 1990), matrix construction (Miles & Huberman, 1994), writing case titles and story summaries (Corbin & Strauss, 2008), and a literature review (Strauss & Corbin, 2008).

Sampling, interviewing, and analysis continued until we reached informational redundancy (i.e., no new themes or patterns were recognized; $n$ = 8); we then enrolled three participants for further sample diversity and to confirm existing findings. One woman was selected for type of health insurance carrier, because health insurance and cost of erlotinib were concerns frequently expressed by the participants. One man was selected for younger age.

Rigor was maintained through vigilant documentation, member checking, dual coder review and discussion of all transcripts, and audit trails. Member checking was conducted by asking three key informants to review and comment on the constructed theory to confirm or refine the interpretive analysis. All three confirmed the substantive theory. In addition, publicly

available information (cancer support websites and personal interest stories) was reviewed and confirmed this process.

## 5.7 RESULTS

The basic psychosocial process constructed from the data is *Surviving Lung Cancer* framed within the context of the participants' recognition of NSCLC as a life-limiting illness without cure (Figure 1).

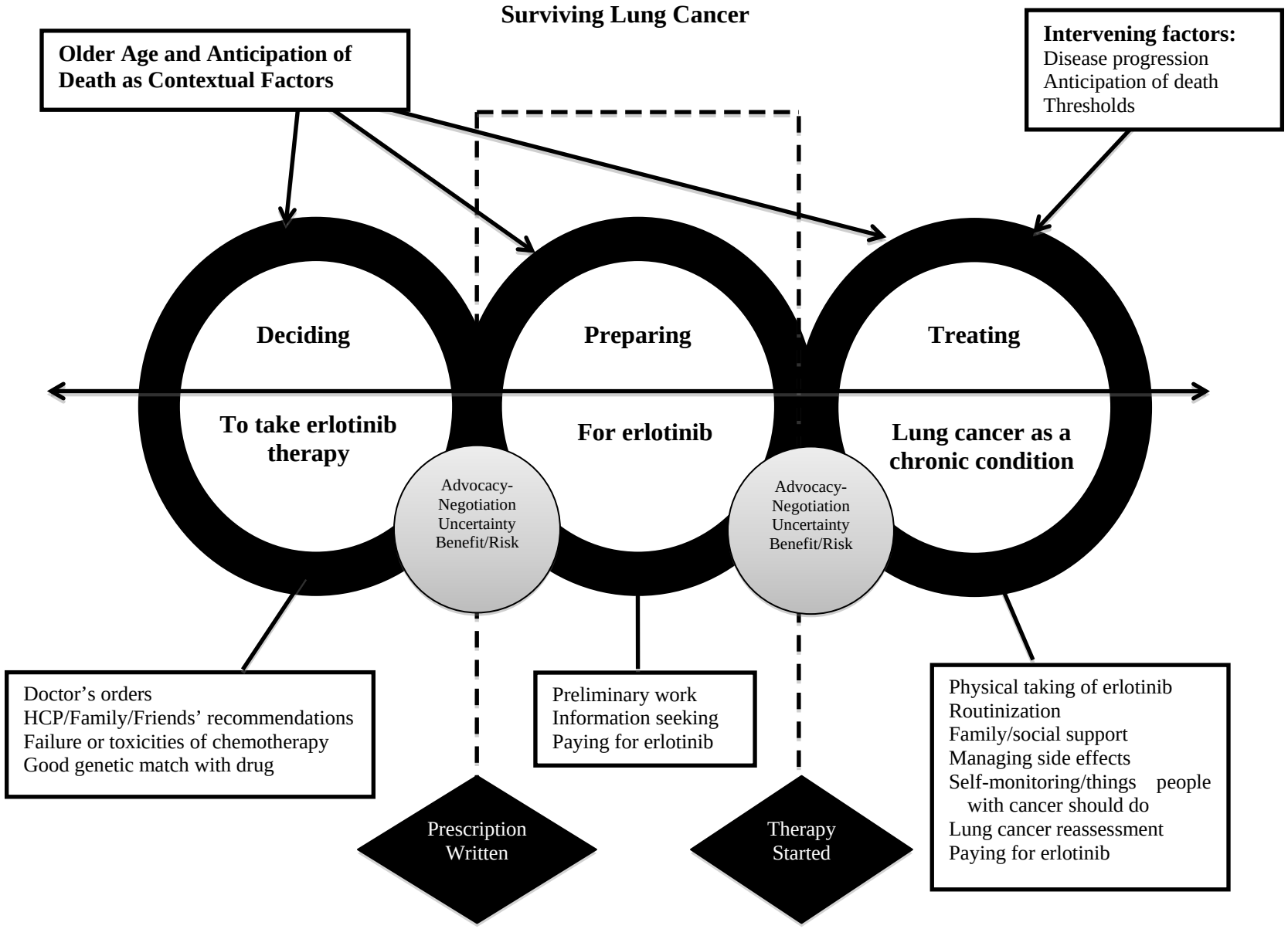


**Figure 1: Surviving lung cancer: Medication-taking and oral targeted therapy**

Title: basic psychosocial process

Circles: main themes

Squares: components of each theme (main tasks, process of each main theme)

Older age and death as contextual factors: occur along the continuum.

Intervening factors: occur usually at one point in time; for participants in this study, the intervening factors occurred during the treatment phase of the medication-taking process.

Double arrow line: represents that while these three phases overlap, they occur on a continuum. There is a beginning and an end to targeted therapy, but with multiple overlapping (or repeating steps) along the way.

Single arrow lines: represents the relationship between the contextual and intervening factors and the three phases.

Dotted lines: represent decision points in the process.

Diamonds: represent the decisions that were made by the participants

Dimensions of the process (grey circles): Constructs that crosscut each phase.

HCP = health care professional (includes oncologists, thoracic surgeons, radiation oncologists, psychiatrist, radiation therapists, infusion nurses, nurses, collaborative nurses, nurse practitioner, physician's assistant, clinical research coordinator, pharmacists, visiting nurse, or other health care providers that take part in the participant's care)

Three dynamic phases comprise the process: (a) *Deciding* to take targeted therapy with erlotinib, (b) *Preparing* for erlotinib, and (c) *Treating* lung cancer as a chronic condition. Each phase includes components that participants addressed before proceeding to the next phase with forward and backward movement affected most often by the cost of erlotinib, disease progression, side effect severity, and/or anticipation of death. The patients' survival is characterized by an ongoing struggle between their recognition of "what will be, will be" despite taking erlotinib every day and their continuing hope for survival.

Nearly all participants (10/13) discussed taking erlotinib as a vehicle for hope of surviving their lung cancer, "If you care and you want to survive this cancer, then you do it." Others referred to erlotinib as "the miracle drug" or a "magic pill" meaning that "it worked (took effect) right away." Managing erlotinib therapy and contending with the hope of a miracle were issues participants faced "24/7." They were surviving NSCLC for a period of time (weeks to years) and all that they managed in taking erlotinib centered on survival. The meaning of survival in the context of a chronic terminal illness differed among the participants ("Just a challenge to see how long I can live" "getting back into the mainstream"), but the process of surviving was similar for all.

> *. . . If I stop the drug the tumors can grow back, so you either take it and deal with any side effects or little inconveniences like having to wear solar protective clothing . . . waiting the hour before you can eat . . . being faithful to taking the medicine, or you throw in the towel, give up and say, "What will be will be," and I'm not going there . . . that's not me.*

### 5.7.1 Deciding to take Erlotinib Therapy

All participants described conditions central to a complicated decision-making process for choosing erlotinib therapy. Some took erlotinib on "doctor's orders," motivated by faith in their

oncologist, “I decided a long time ago to put my faith in Dr. (oncologist). And when he said, ‘this is what I think you should do,’ that’s what I did.” Other participants initiated erlotinib therapy based on the combined advice of their clinical team, family, and/or friends.

> *I don’t know if it’s blind faith…when I was first diagnosed, and you’re talking to various people about where to go, and everybody has some advice for you to go to Texas, go to Ohio . . .and I felt like [cancer treatment center] had a good reputation . . . I think it was a neurologist that I saw where this all started, and she recommended [surgeon] and [oncologist] because they had good reputations . . . plus we had a friend in Philadelphia that works for [pharmaceutical company], and she knows all the doctors there, and they knew [oncologist] and spoke highly of him. So it was all of these things kept leading back to [oncologist] . . .*

Unacceptable toxicities or failure of other therapies were also conditions for starting erlotinib therapy. For example, a woman took erlotinib after seven other therapies:

> *I was able to tolerate it (chemotherapy) but . . . he (oncologist) said I can’t stay on it forever . . . he said to switch to the Tarceva® because I was starting to get numbness (from chemotherapy) . . . a little bit. The neuropathy in the hands and the feet-just a little bit but he said it’s irreversible if it gets too bad.*

Participants also took erlotinib because of an identified or presumed genetic mutation, framing this genetic compatibility as “what works best with my NSCLC.” Most were aware of their mutation status and some specifically sought erlotinib treatment. A participant’s daughter described:

> *I had read a lot on there [a cancer website] about Tarceva® and the EGFR mutation . . . which is why we asked the doctor to test him for it because I tested positive for it-and I guess generally they won’t test somebody at his age group [80s] for it- but because there was a family history they tested. And he did test positive.*

A man who took erlotinib for over two years summarized the considerations in his treatment decision-making process as follows:

> *I told my doctor . . . if he couldn’t improve on the first two experiences [chemotherapy], then I wanted to switch over to Tarceva®. And I came in with the knowledge about Tarceva-my cousin . . . had been on Tarceva® for three years. And the median longevity the doctor said was eleven months . . . so I was encouraged because its effectiveness kind of varied according to genotype . . . indeed I had a good match with the drug.*

### 5.7.2 Preparing for Erlotinib

Preparing to take erlotinib refers to undertaking steps toward obtaining and managing erlotinib, framed by the participants as "preliminary work."

> *It's concerning . . . there's so much preliminary that goes: first of all securing it . . . and then when you get it and read the directions, it's, "keep it at certain temperature," and, "wash your hands after taking the pill," which I have never heard of before. So, just in, preparing and getting the pill . . . there is enough to let you know that this is something beyond an aspirin.*

This man's description is evidence that the preparing phase serves to alert participants to the importance of erlotinib. Preparing for erlotinib included finding a specialty pharmacy, securing the medication through mail order, and deciphering the directions for taking erlotinib such as, "avoid grapefruit juice" or "I can't sit in the sun." Often, the directions for taking erlotinib were a hint for its potency:

> *It's an extremely powerful drug . . . of course when you get the drug, it tells you when you handle it, to wash your hands. That's my first tip-off, "Hmm, ok, I should keep these in their own little bottle."*

The participants obtained information about what erlotinib does, how to take it, and how to get it from brochures, books, and/or a starter kit. Some participants deliberately avoided searching the Internet for information because "sometimes, not knowing is better." Others searched the Internet but were selective, "I go there (American Cancer Society) or I look in the information from (cancer center) … I just don't get on and read . . . because I think there's a lot of false information out there."

Paying for erlotinib was at the heart of the preparing phase. Nearly all participants referred to the high cost, "It's expensive. I want them to know that." Many felt the cost of erlotinib was prohibitive. A woman who stopped taking erlotinib due to expensive co-payments affirmed:

*Most patients figure it's not worth it if you're dying, you have cancer. Some would like to live but where's the funds for you to survive? You can't. They'll break you, I tell you, this medication will break you . . . if you have to pay for it without insurance. It will break you in no time. In no time . . . Even if you pay with insurance, it's (the cost) still high.*

Four participants received financial assistance either to pay for erlotinib or to defray the cost of prescription co-payments, but several struggled to obtain financial assistance and approval, "Well . . . the first time, the insurance kept denying it. And my son . . . works for Medicare . . . he's the one that suggested, 'Write a letter to the foundation' . . . they can only say no.'" A daughter described her experience in obtaining funds for her father's medication:

*They (health insurance company) decided they would cover 10% of it. Well 10% of $5000 is [leaves] a lot of money every month [to pay] . . . I talked with [foundation oncologist]…and he got me in touch with the [foundation]…once they got that paperwork and approved that **yes**, he did need the medication, and agreed that **yes**, he could take it first-line… literally within days they called, and said, "Ok, your dad's been approved" . . . "alright, what's his co-pay?" "Zero." And I was, "Are you kidding me?"*

Securing payment assistance approval for erlotinib resulted in a treatment delay ("So I got on the pill about 30 days later"), one that was not always apparent to the clinical team ("I don't think that they [doctors] realize . . . he probably thought that I went to the pharmacy and got it"). Not meeting the assistance criteria and increasing drug prices added additional challenges for the participants. Furthermore, taking two strengths of erlotinib requires two co-payments, adding an additional expense for a patient. In one case, the co-payment influenced the erlotinib dose that was acceptable to the patient, " . . . You pay for 100 (mgs), and then 25 (mgs), there're two prescriptions. There's two co-payments there. So it costs a lot more. So if I go back to 150 (mg) then it's just one co-payment."

### 5.7.3 Treating Lung Cancer as a Chronic Condition

The culmination of successfully navigating the *deciding* and *preparing* phases was advancement to *treating* lung cancer as "a chronic condition." This phase represented the day-to-day challenges the patients experienced related to taking erlotinib and involved their recognition of the chronicity of therapy ("We need to see where this drug will take me and it'll give me a break from [chemotherapy]. (The doctor's) not guaranteeing that there's going to be any, you know—he's just looking for maintenance." "I don't think that Tarceva will totally eradicate my lung cancer . . . but it's . . . making things not grow"). Treating NSCLC as a chronic condition included one's recognition of his/her ownership of the process of taking medication, "So I want to make sure that it's effective by following . . . the directions and . . . if it says to take it the same time every day I want to be sure that I take it the same time every day."

The mechanics of taking erlotinib daily often included comparison to an over-the-counter medication, such as aspirin or iron tablets, "My iron tablet was worse, so I haven't been taking those, but no, I haven't really had too much of an adjustment." All participants described routinization, the process by which taking erlotinib became a habitual or consistent practice, "It's a matter of discipline." Routinization was associated with timing erlotinib with an empty stomach (e.g., 2 hours before breakfast), a location (e.g., bedside table, dresser, living room table), time of day (e.g., AM or PM), and/or a storage strategy (e.g., pill minder or pill bottle). Routinization also involved the use of an alarm or other reminder (e.g., cats awaken a woman), visual aid (e.g., clear glass on a table filled with medication), or a physical or active cue (e.g., moving pill bottles from the front to the back of a table) to take erlotinib.

Women who lived alone used a calendar or a steno pad to track their doses of erlotinib, while participants who lived with a spouse tended to rely on the storage strategy as a means of a

"checks and balances" system for remembering to take erlotinib. One woman admitted that she occasionally missed a dose ("I'm human, I miss some days"); however, most indicated that they never had difficulty remembering to take erlotinib because they associated it with a storage strategy and a location ("I know because it's all in that jar, it's all in that little glass that I put on the kitchen counter, so there's no questioning later on"), time of day ("'Cause it is the first thing that I do in the morning"), or a proactive refilling strategy. Men often indicated that they never forgot to take erlotinib because their wives either prepared or gave it to them, so "there's no question that the transaction takes place."

Participants recognized a need for "having help" in their daily survival. They described/found support from their family or friends, Internet blogs and chat rooms, and/or pets. Family/social support included both assistance with taking medication and active participation in special family connections, living the family moments, and being involved in the present. Enjoyment of family time served as further motivation for taking erlotinib daily (e.g., to see a grandson play baseball). The participant's and his/her family's prior experiences with cancer (e.g., spouse or parent who died from cancer) colored how they interacted with each other during their process of surviving lung cancer. These patients shared a perceived survival obligation to family members, friends, or prior research participants and to those who have died.

> *. . . my brothers want me to survive this cancer, I guess maybe if I can survive this long, they want me to survive a little longer. . . and I shouldn't let them down.*

The medication has unique side effects related to inhibition of the EGFR pathway. All participants experienced side effects and recognized this as a part of managing the disease. The most commonly reported side effects were rash, diarrhea, stomach cramping/gastrointestinal upset, nail issues (e.g., nail splitting), eye itching, long eyelashes ("it looked like spider legs, it was wild"), hair changes, nausea, and fatigue. Rash and diarrhea were referred to as "social

inhibitors". The "social inhibitors" were especially bothersome and stigmatizing if one was working full-time:

> *The biggest thing is you become . . . a little self-conscious because you know your face is all splotchy or red, and, although I've seen some of the pictures where it's very severe-thank God I haven't gotten to that point, but you know, it's a little bit of a pain . . . I don't want people looking at me, so it's almost like I cover it (rash) up because it's just treat me like I'm the same old person and not "Hey, there's a cancer guy."*

Several participants (5/13) had reductions in their erlotinib dose due to side effect severity:

> *I reached a point about 2 months into it where everything was changing…I said to my husband, "What's on this sandwich?" . . . "It's burning my mouth" . . . I noticed things burned when I ate, everything was hot to me, in my mouth, spicy hot . . . I went in, and I said, "I can't take this drug, I can't eat. Everything is hot to me in my mouth. And (oncologist) said, "no, no, no, no, no, you're doing so good. We'll lower the dose, we'll put you on 100 mg dose." I said, "OK, I'm willing."*

Despite the severity of side effects, the participants expressed their commitment to taking erlotinib, "You know if it's keeping me alive, I'll accept it." While some admitted to skipping a dose when they experienced a distressing side effect, others perceived the rash as a hallmark for the effectiveness of erlotinib, " . . . I didn't have the rash, but I've had a few pimples . . . and so I feel like because I have the side effects it must be working."

Surviving lung cancer included rigorous self-assessment, self-maintenance, and external assessments required of one with advanced cancer. All participants discussed the role of exercise (e.g., swimming, Jazzercise), nutrition, routine health screenings (e.g., mammograms), prevention of EGFR inhibition-related side effects (e.g., sun protective clothing, lotion without alcohol), and self-examination for new or worsening side effects as crucial activities for surviving lung cancer. Periodic reassessments of lung cancer could prompt an increase in the dose of erlotinib, no change in dose, or discontinuation of therapy. Participants discussed the

importance of “keeping busy” and “staying active” as a means of engaging the body and mind in their survival, particularly the older participants, “I’ve been really busy. I’m always busy. I like to be busy. I don’t want to sit around and—so.”

> *If you have a lot of exercise, you don’t feel the effects of the drug so much. But if you don’t exercise, you feel it all the time. For some reason, you can’t take your mind off of it. And I think it’s partly psychological . . . I don’t feel good, I pack my swim bag and I go out. If I don’t feel good at the swimming pool . . . I go out for a walk. You find something other than your own illness to look at . . .*

Paying for erlotinib was an ongoing struggle during the maintenance phase of the medication-taking process. Some became acutely aware of the cost associated with each pill, “Ok, I’m going to stick this in my mouth and this is $200, and I don’t want to waste it.” Difficulty with paying for erlotinib was particularly evident in the extreme case of a survivor who stopped taking erlotinib due to co-payments that had increased from $60 to $600 over a 6-year period for a 90-day 100 mg prescription. Stopping erlotinib due to cost can be heartbreaking because the medication “gives you hope” and discontinuing it “takes that hope away.”

After a woman mentioned the need for support groups for individuals who take erlotinib as a means for sharing experiences, we added a question about peer support groups to the interview guide. Subsequent participants concurred, “That’s the truth. I agree. I wish I had had someone to talk to.”

> *I definitely think it would have . . . no information has ever been given to us regarding small groups for lung cancer, lung cancer families, or Tarceva-taking patients. All of that would have been helpful. I don’t think there is a lot of that out there.*

Women who attended other types of support groups (e.g., American Cancer Society’s “Look Good, Feel Better” program), who had previous experiences with treatment with an intravenous EGFR inhibitor, or who began taking erlotinib immediately after approval (2004) by the Food and Drug Administration did not feel a lung cancer-specific support group would have

been helpful unless participants were grouped according to similar characteristics such as age, race/ethnicity, or time on therapy.

### 5.7.4 Dimensions of the Process

As analysis progressed it was evident that several dimensions of the survival process crosscut all phases, particularly advocacy and the related negotiation required for daily survival especially when weighing the benefits versus the risks of erlotinib therapy. Negotiating by the participant or by a family member or clinician on behalf of the participant was evident in every phase of the process. In particular, advocacy occurred on a continuum, ranging from a very active between a participant and a clinician to a more directive role, "You have to be very active in your own care."

> *I just asked him [oncologist] to lower it [dose of erlotinib]. I said I "don't feel comfortable with it" so I just asked him to just lower it. It didn't know what was bothering me, but something was bothering me. So I told him to lower it.*

Constant uncertainty related to the cause of side effects or of lung cancer, who to go to for information or treatment, or next steps in treatment ("where do we go from here?") produced a longing for living life to the fullest because "you never know when your ship's going down". Participants discussed the wish for "quality of life, not quantity" or "feeling normal." Family was central to living life to the fullest for these survivors who described prioritizing family time, planning exotic family vacations, and relishing "ordinary" events such as a grandchild's baseball game.

### 5.7.5 Contextual Factors: Older Age and Death

Older age provided context to surviving lung cancer. Participants recognized the vulnerability associated with being one who is aging with a terminal disease as both a barrier to and a reason for starting therapy and as a confounding factor in determining the causality of side effects or other symptoms. Age provided context to self-management of NSCLC for an older adult (especially a single older adult) on a fixed income who was facing challenges with diet, obtaining nutritious foods, meal preparation, exercise/activities, and payment for long-term medication. This was particularly significant when discussing the need for going to extremes to pay for erlotinib, "I wanted to exhaust all that (options) first and then use my retirement money."

"Death talk" was common in all interviews and provided additional context for participants' view of survival. Death talk referred to spoken or unspoken reference to anticipating death and was regularly intertwined with discussions about family and friends.

> *[Spoken tearfully] When they (grandchildren) leave I come in the house and I cry because I just have so much fun with them. It's not because I have cancer-it's because I just have so much fun and that's how I want them to remember me.*

Surviving to the fullest in the time the participants had remaining was key because "it could end in a year or two." Death talk occurred in almost all interviews, but was more prominent in the final interview. Anticipation of death appeared in all points of the survival process, beginning with starting erlotinib therapy ("they told me it was eleven to twelve months median [survival]") to treating lung cancer as a chronic condition:

> *I've survived longer than they've thought, I guess. I remember the first year, I was diagnosed in the fall, the gardener puts in tulips, and I said to him, "I hope I see them in the spring." You know, I did. And I'm very grateful.*

### 5.7.6 Intervening Factors

Factors occurring at one point in time during the surviving process, such as disease progression, anticipation of death, and real or hypothetical "thresholds" for reduction in dose, interruption, or discontinuation of erlotinib could derail taking erlotinib. Thresholds referred to reaching one's limit; some participants had reached theirs at the time of their interview, while others knew what their limits would be but had not yet reached them. Actual thresholds included cost of erlotinib and side effect severity (e.g., rash, diarrhea, dehydration). Two participants stated that experiencing pain related to cancer would lead to stopping erlotinib. The potential for worse side effects with higher doses of erlotinib frequently brought feelings of dread:

> *It's a dread, I guess, it's a dread of taking you know the 75 mg (from 50 mg) . . . I'll just have to wait and see . . . because if the 75 makes me worse-or feel worse, I may just say "The hell with it."*

## 5.8 DISCUSSION

Our purpose was to develop a substantive theory that explained the process of medication-taking for individuals with NSCLC receiving oral EGFR inhibitor therapy. "Surviving lung cancer" was grounded in the data and fit the participants' descriptions of their medication-taking process, which included deciding to take erlotinib, preparing to take an expensive and powerful daily oral medication for treatment of NSCLC, and treating lung cancer as a life-limiting chronic condition. Each distinct phase had crosscutting dimensions such as advocacy and uncertainty. Our findings illustrate the active participation and sacrifice that patients with NSCLC willingly endure in taking this class of medication.

We sought to understand *how* persons with NSCLC actually took erlotinib daily, rather than whether or not they took it as prescribed (McCoy, 2009). In their descriptions of surviving lung cancer, our participants voiced comparable aspects of medication-taking to those reported in grounded theory studies of older adults with heart disease (Chen et al., 2007) such as perceived effectiveness of medication (how well it works), developing partnerships with and trust in their health care team, and seeking and sharing information. Consistent with Gray's (2006) study of persons living with human immunodeficiency virus, our participants realized the benefits of therapy and made a conscious decision to live through taking a ongoing therapy; however, published reports of grounded theory studies for persons with chronic conditions often use the terms "adherence" (following a regimen as prescribed) (Haynes et al., 2008) and "medication-taking" (the work of adherence) (McCoy, 2009) synonymously. Unlike these reports, our findings describe not only the work required to take the medication, but also the processes and motivation required to survive a chronic terminal disease. The "adherence lens" excludes exploration of the meaning of the medication to participants and the larger social-psychological context within which medication-taking occurs. Our previous study of women with early stage breast cancer receiving therapy with an aromatase inhibitor, anastrozole, examined medication-taking and discovered that value/importance of medication, side effect severity, and medication self-management were primary constructs in medication self-management in the early phase of breast cancer survivorship (Wickersham et al., 2011). These constructs are amplified in the case of persons with NSCLC for whom procuring erlotinib, sustaining erlotinib therapy, managing side effects, and spending time with family were key components to surviving lung cancer.

Older age and anticipation of death provided context to the stories of the participants' surviving process. Medication-taking processes included aspects of self-care for older adults with

a chronic life-limiting disease on fixed incomes who face challenges with meal preparation, diet, obtaining nutritious foods, exercise, activities, and payment for erlotinib. Anticipation of death was an undercurrent for all participants, but appeared more in the forefront when erlotinib was no longer effective in treating their lung cancer.

The findings provide strong evidence for revisiting the definition of cancer survivorship, a term with inconsistent operational definitions (Khan et al., 2012). The National Coalition for Cancer Survivorship defines "cancer survivor" as one "from the moment of diagnosis and for the balance of life," whereas the National Cancer Institute (2012) defines survivorship as focusing on the physical, psychosocial, and economic aspects of health and life post-treatment until end of life. Furthermore, the traditionally implemented five-year cut-off point does not apply for those with cancer who die within the first year of diagnosis (Kahn et al., 2012), such as patients with NSCLC (16% 5-year relative survival; Siegel et al., 2012).

Regardless of the definition, "cancer survivor" usually infers one who is cancer free (Mullan, 1985). This was not true for our participants with advanced NSCLC. Our findings were similar to that of Kagan (1997) regarding older adults with cancer who were "integrating cancer into a life mostly lived" (p. 43). Our participants' process concerned living with, managing, and integrating cancer into their daily lives (Kagan, 1997). The identification of thresholds for which older adults with NSCLC determine under what conditions one will or will not live with erlotinib therapy is also similar to Kagan's (1997) findings. Our participants' process adds to existing knowledge by including the economic realities of survivorship. Their narratives exemplified the tension between knowing the limits of treatment for a condition that is unlikely to be cured and their own limits with taking that treatment (e.g., cost, side effect severity). Family and social support went beyond medication assistance; rather, social support encompassed living in the

moment and cherishing family time. Family history influenced patients' response to cancer and underscored the importance of surviving for as long as possible for friends or family members who did not or could not survive themselves.

Our findings should be interpreted in light of several limitations to the study. The sample was obtained from a single cancer center. Purposive sampling to maximize variation of participants was used to minimize this limitation. Our participants were similar in age and racial/ethnic make-up to the national NSCLC population (American Cancer Society, 2012); however, our sample included more women than men. Additionally, almost half of our participants had a documented EGFR mutation; the participants' awareness of their mutation status may have led them to be more committed to treatment with erlotinib. To address these potential limitations, the developing theory was shared with key participants and clinicians at the cancer center to best understand comparability and transferability of the findings.

Our findings provide the theoretical foundation for development of a tailored intervention for improving medication-taking. The most striking implications of this study are in the areas of affordable care and prescribing practices. High costs of medication and prescription co-payments were thresholds for treatment discontinuation for some and a source of concern for all. Several participants, specifically older women who lived alone, charged the PI with addressing this issue. Plans for long-term survivorship for one with advanced NSCLC should include a plan for affordable care and access to medication over time because insurance benefits may change or reach limits. Current avenues for long-term access are unclear. Further study of cost and self-advocacy as they relate to medication-taking, surviving NSCLC, and health policy is critical. Furthermore, we learned that patients manage two co-payments for two strengths of erlotinib (one co-pay for each strength). It is unclear whether this is due to usual practice or pharmacist

preference. Higher prescription co-payments have been associated with both nonpersistence and nonadherence to oral hormonal therapy for women over the age of 65 with early-stage breast cancer (Neugut et al., 2011). Assessment of access to medication is still needed for older men and women with advanced NSCLC on a fixed income. Moreover, clinicians must reassess the patient's access to medication over time as insurance benefits may change or reach limits.

We present the participants' stories of surviving lung cancer, but the clinician perspective is an integral part of that story. Given the central role that clinicians play in assisting with procurement and maintenance of therapy and the suggestion from these data that clinicians may not be fully aware of cost and access to treatment problems, further studies of medication-taking that include the clinician perspective are needed.

Generally, participants endorsed peer support groups for persons with NSCLC taking therapy with erlotinib. This suggests that support groups or group interventions based on select characteristics (e.g., gender, age, time in therapy) that address medication-taking and navigating concerns of survivorship are indicated for individuals with NSCLC.

We sought to explore the process of medication-taking for persons with NSCLC receiving therapy with an oral EGFR inhibitor. We developed a substantive theory that explains the process of medication-taking as it relates to patient survival of NSCLC. Our results contribute to understanding how persons with NSCLC view themselves, the work they do to take an oral EGFR inhibitor, and their daily process of surviving lung cancer.

## 5.9 REFERENCES


Aisner, J. (2007) Overview of the changing paradigm in cancer treatment: Oral chemotherapy. *American Journal of Health-System Pharmacists*, 64(Supp 5), S4-S7. doi: 10.2146/ajhp070035

The American Cancer Society. (2012) Lung cancer (Non-small cell). Retrieved July 11, 2012 from http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf.

Bezjak, A., Tu, D., Seymour, L., Clark, G., Trajkovic, A., Zukin, M., … Shepherd, F. A. (2006) Symptom improvement in lung cancer patients treated with erlotinib: Quality of life analysis of the national cancer institute of Canada clinical trials group study BR.21. *Journal of Clinical Oncology*, 24(24), 3831-3837. doi: 10.1200/jco.2006.05.8073

Chen, C. -H., Wu, J. -R., Yen, M., & Chen, Z. -C. (2007) A model of medication-taking behavior in elderly individuals with chronic disease. *Journal of Cardiovascular Nursing*, 22(5), 359-365. doi: 10.1097/01.JCN.0000287029.87746.58

Erlen, J. A. & Happ, M. (2006) Patients with Alzheimer's disease who live at home: The challenge of medication taking. Podium presentation presented at the *18th Scientific Sessions of the Eastern Nursing Research Society*, Philadelphia, PA.

Ersek, M., Krapbill, B. M., & Du Pen, A. (1999) Factors hindering patients' use of medication for cancer pain. *Cancer Practice*, 7(5), 226-232.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975) "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189-198.

Gray, J. (2006) Becoming adherent: Experiences of persons living with HIV/AIDS. *Journal of the Association of Nurses in AIDS Care*, 17(3), 47-54. doi: 10.1016/j.jana.2006.03.004

Kagan, S. H. (1997). *Older adults coping with cancer: Integrating cancer into a life mostly lived.* New York: Garland Publishing, Inc.

Kahn, N. A., Rose, P. W., & Evans, J. (2012) Defining cancer survivorship: a more transparent approach is needed. *Journal of Cancer Survivorship*, 6, 33-36. doi: 10.1007/s11764-011-0194-6.

Landier, W., Hughes, C. B., Calvillo, E. R., Anderson, N. L. R., Briseno-Toomey, D., Dominguez, L., … Bhatia, S. (2011) A grounded theory of the process of adherence to oral chemotherapy in Hispanic and Caucasian children and adolescents with acute lymphoblastic leukemia. *Journal of Pediatric Oncology Nursing,* 28(4), 203-223. doi: 10.1177/1043454211409582

Malbasa, T., Kodish, E., & Santacroce, S. J. (2007) Adolescent adherence to oral therapy for leukemia: A focus group study. *Journal of Pediatric Oncology Nursing,* 24, 139-151. doi: 10.1177/1043454206298695

McCoy, L. (2009) Time, self and the medication day: a closer look at the everyday work of 'adherence.' *Sociology of Health and Illness,* 31(1), 128-146. doi: 10.111/j.1467-9566.2008.01120.x

Miles, M. B. & Huberman, A. M. (1994). *Qualitative data analysis: an expanded sourcebook* (*2nd ed*). Sage: Thousand Oaks, CA.

Miller, V. A., Riley, G. J., Zakowski, M. F., Li, A. R., Patel, J. D., Heelan, R. T., … Johnson, D.H. (2008) Molecular characteristics of bronchoalveolar carcinoma and adenocarcinomas, bronchoalveolar subtypes predict response to erlotinib. *Journal of Clinical Oncology,* 26, 1472-1478. doi: 10.1200/JCO.2007.13.0862

Mullan, F. (1985) Seasons of survival: Reflections of a physician with cancer. *New England Journal of Medicine,* 313(4), 270-273.

National Cancer Institute. (2012) Dictionary of cancer terms. Retrieved July 10, 2012 from http://cancer.gov/dictionary?cdrid=445089.

National Coalition for Cancer Survivorship. (2012) Retrieved July 25, 2012 from http://www.canceradvocacy.org/.

National Comprehensive Cancer Network (NCCN). (2011) Practice guidelines in oncology™: Non-small cell lung cancer. V3.2011. Retrieved April 4, 2011 from http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Neugut, A. I., Subar, M., Wilde, E. T., Stratton, S., Brouse, C. H., Hillyer, G. C., … Hershman, D. L. (2011) Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *Journal of Clinical Oncology,* 29(18), 2534-2542. doi: 10.1200/JCO.2010.33.3179

Russell, C. L., Kilburn, E., Conn, V. S., & Ashbaugh, C. (2003) Medication-taking beliefs of adult renal transplant recipients. *Clinical Nurse Specialist,* 17(4), 200-208.

Sandelowski, M., Holditch-Davis, D., & Glenn Harris, B. (1989) Artful design: Writing the proposal for research in the naturalist paradigm. *Research in Nursing and Health*, 12, 77-84.

Sequist, L. V., Martins, R. G., Spigel, D., Grunberg, S. M., Spira, A., Janne, P. A., …Lynch, T. J. (2008) Gefitinib in patients with advanced non-small cell lung cancer harboring somatic EGFR mutations. *Journal of Clinical Oncology*, 26, 2442-2449. doi: 10.1200/JCO.2007.14.8494

Siegel, R., Naishadham, D., & Jemal, A. (2012) Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians,* 62(10), 10-29.

Spreen, O. & Strauss, E. (1998) *A compendium of neuropsychogical test: Administration, norms, and commentary*. New York: Oxford University.

Wickersham, K., Happ, M. B., & Bender, C. M. (2011) Self-reported side effects and side effect severity regarding medication-taking for women with breast cancer taking oral aromatase inhibitor therapy [Abstract BU]. *Oncology Nursing Forum,* 38(1), A1-A90. doi: 10.1188/11.ONF.E60

# 6.0 SUMMARY

Our purpose was to describe the medication-taking process of and to identify factors influencing medication-taking for adult men and women with NSCLC who were receiving therapy with an oral EGFR inhibitor. Using grounded theory methodology and analyses (Strauss & Corbin, 2008; Glaser & Strauss, 1967) we developed a substantive theory for individuals receiving therapy with erlotinib that explained their process of medication-taking. Thirteen participants were purposively selected for variation in gender (5 men/8 women), race/ethnicity (2 non-whites), age (52-83 years), time in therapy (1 week to 6 or more years), dose reductions ($n$ = 5), and therapy discontinuation ($n$ = 2). Theoretical sampling focused on age and health insurance carrier. Data were collected through 32 semiformal and brief interviews concerning one's medication-taking behaviors related to therapy with oral EGFR inhibitors from July 22, 2011 to August 6, 2012. We employed constant comparative and dimensional analyses. The basic psychosocial process, *Surviving Lung Cancer*, which participants framed within the recognition of NSCLC as a life-limiting illness without cure, included a dynamic process of (a) *Deciding* to take targeted therapy with erlotinib, (b) *Preparing* for erlotinib, and (c) *Treating* lung cancer as a chronic condition. Older age and anticipation of death provided context to the stories of the participants' surviving process. Participants identified real or potential thresholds that would determine the conditions under which one would or would not live with erlotinib, including cost of erlotinib, side effect severity, and pain related to cancer. Three key informants were selected to review and comment

on the constructed theory to confirm or refine the interpretive analysis, who confirmed the conceptual model. We reviewed public websites (e.g., Cancer Grace and Inspire), which demonstrated that patients with advanced stage NSCLC have similar concerns about treatment for lung cancer and management of side effects and provided external validation of the psychosocial process. Findings were shared with the clinical team, who confirmed the difficulty that patients encounter in paying for erlotinib and with managing side effect severity. Findings were also shared with the infusion nursing staff of the second floor treatment are of the cancer center, who confirmed the study results.

# 7.0 LIMITATIONS

Our findings should be interpreted in light of several limitations to the study. First, the sample was obtained from a single cancer center. Purposive sampling to maximize variation of participants was used to minimize this limitation. However, it is possible that patients from more rural areas may have responded differently. Second, when compared to the national population of patients with NSCLC, our participants were similar in age and racial/ethnic make-up (American Cancer Society, 2012); however, our sample included more women than men. On reflection, it could be that women were more likely to share their stories than men. The findings of the study were shared with two women and one man to mitigate this potential limitation. All three participants confirmed the findings. Third, about 10% of patients with NSCLC have a mutation in the EGFR gene that is associated with better response to an oral EGFR inhibitor (Fukuoka et al., 2003; Kris et al., 2003). In our study, almost half of our participants had a documented EGFR mutation. Quite possibly the length of survival we saw in our patient sample was colored by the number of participants with the mutation. In addition, their awareness of their mutation status may have influenced their commitment to treatment with erlotinib. To address this potential limitation, the developing theory was shared with both key participants and clinicians at the cancer center to best understand comparability and transferability of the findings.

# 8.0 CONCLUSIONS

We sought to explore the process of medication-taking for persons with NSCLC receiving therapy with an oral EGFR inhibitor. Using qualitative data obtained through 32 interviews with the 13 participants, we developed a substantive theory, *Surviving Lung Cancer,* that explains the process of medication-taking as it relates to the participants' survival of NSCLC. Our results contribute to understanding how persons with NSCLC view themselves, the work they do to take an oral EGFR inhibitor, and their daily process of surviving lung cancer.

# 9.0 IMPLICATIONS

Our results provide the theoretical foundation to guide future research concerning medication-taking for individuals receiving therapy with an oral EGFR inhibitor with the goal of development of a tailored intervention for improving medication-taking. First, our results challenge the generally accepted definition of cancer survivor as one who has finished treatment for cancer. The paradigm shift to the use of more oral targeted therapies for persons with NSCLC also shifts the definition of cancer survivor from post-treatment to one who is integrating oral targeted therapy into daily life. Exploration of survivorship for persons with NSCLC is indicated, including comparisons to individuals with long-term conditions that have acute exacerbations (e.g., pulmonary fibrosis, acute respiratory distress syndrome) and to individuals with other types of cancer who are receiving oral targeted therapy (e.g., leukemia, breast cancer).

Second, the most striking implications of this study are in the areas of affordable care and prescribing practices. High costs of medication and prescription co-payments were thresholds for treatment discontinuation for some and a source of concern for all. Several participants, specifically older women who lived alone, charged the PI with addressing this issue. Plans for long-term survivorship for one with advanced NSCLC should include strategies for affordable care and access to medication over time because insurance benefits may change or reach limits. Current avenues for long-term access are unclear. Further study of cost and self-advocacy as they relate to medication-taking, surviving NSCLC, and health policy is needed. Furthermore, we

learned that patients manage two co-payments for two strengths of erlotinib (one co-pay for each strength). It is uncertain whether this is due to usual practice or pharmacist preference. Assessment of access to medication is still needed for older men and women with advanced NSCLC on a fixed income.

Third, all participants provided rich description concerning the side effects they experienced, side effect severity and management, and thresholds for discontinuing therapy with erlotinib. Five participants had reductions in their dose of erlotinib due to side effect severity, and at least one participant recognized skin toxicity as a proxy marker for clinical effectiveness of erlotinib. Such findings have been reported in the literature (Eames et al., 2010); however, an explanation for the relationship between the rash and response to EGFR inhibitor therapy is elusive (Amador et al., 2004). Genetic differences among individuals have been suggested as potential reason for this relationship (Amador et al., 2004). Given that persons with an EGFR mutation are more likely to respond to therapy (Miller et al., 2008; Sequist et al. 2008), exploration of the individual susceptibility to side effects for patients with cancer who are receiving an oral EGFR inhibitor may be indicated as a first step to further understanding who may be at risk for difficulty with taking their oral EGFR inhibitors.

Age provided context to self-management of NSCLC for an older adult (especially a single older adult) on a fixed income who was facing challenges with diet, obtaining nutritious foods, meal preparation, exercise/activities, and payment for long-term medication. We also noted some gender differences in medication-taking of erlotinib; for example, men described taking erlotinib therapy in partnership with their spouse, but most women (5 were married) managed erlotinib alone. Future studies examining differences between older and younger

individuals as well as men and women are needed to further understand medication-taking with oral EGFR inhibitors.

We present the participants' stories of surviving lung cancer, but the clinician perspective is an integral part of that story. Given the central role that clinicians play in assisting with procurement and maintenance of therapy and the suggestion from these data that clinicians may not be fully aware of cost and access to treatment problems, further studies of medication-taking that include the clinician perspective are needed.

Generally, participants endorsed peer support groups for persons with NSCLC taking therapy with erlotinib. This suggests that support groups or group interventions based on select characteristics (e.g., gender, age, length of time on therapy) that address medication-taking and navigating concerns of survivorship are indicated for individuals with NSCLC.

Taken together, our findings provide direction for steps toward development of a tailored intervention for improving medication-taking for oral EGFR inhibitors for persons with NSCLC. These steps include the following possible studies: (a) a concept analysis of cancer survivorship for persons with NSCLC that includes comparisons to individuals with other long-term conditions with acute exacerbations (e.g., pulmonary fibrosis, acute respiratory distress syndrome) and to individuals with other types of cancer taking oral targeted therapies (e.g., breast cancer, leukemia, melanoma); (b) a qualitative descriptive study exploring clinicians' perspectives of medication-taking, to be conducted at the same NCI-designated cancer center where our participants were recruited as well as at a second academic NCI-designated cancer center for comparison of findings; (c) a descriptive correlational study exploring individual susceptibility to side effects for patients with cancer who are receiving an oral EGFR inhibitor as a first step to further understanding who may be at risk for difficulty with taking their oral EGFR

inhibitor; (d) a descriptive cohort study, stratified by age and gender, examining potential patient- (e.g., age, gender, race/ethnicity, level of education, co-morbidities, concomitant medications, depressive symptoms, anxiety, fatigue), illness- (e.g., cancer type and subtype, stage, prior therapy for cancer), treatment- (e.g., side effects and side effect severity), and socially-related (e.g., advocacy, type of health insurance, prescription plan assistance, access to medication and health care) predictors of medication-taking with oral EGFR inhibitors; (e) development and pilot-testing of a theoretically-based tailored intervention that includes peer support or group interventions and the combined findings from the first four studies; and (f) a randomized controlled trial examining the effectiveness of the pilot-tested (adjusted as appropriate) theoretically-based tailored intervention for improving medication-taking with oral EGFR inhibitors. Findings from these studies may also lay the foundation for exploration of medication-taking for individuals with NSCLC receiving a different class of oral targeted therapy, such as crizotinib (Xalkori®, Pfizer, New York, NY) which targets EML4-ALK, and for individuals with other types of cancer who are receiving oral targeted therapies, such as persons with melanoma with a mutation of the *BRAF* gene who are taking vemurafenib (Zelburaf®, Genentech, San Francisco, CA).

# APPENDIX A

## UNIVERSITY OF PITTSBURGH CANCER INSTITUTE

## PROTOCOL REVIEW COMMITTEE (PRC) APPROVAL LETTER

UPMC Cancer Centers *and*
University of Pittsburgh Cancer Institute

Brandon Kaukus
Research Project Clinician
Clinical Research Services
Hillman Cancer Center - Fourth Floor
5115 Centre Avenue
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Fax: 412-647-0949
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# MEMORANDUM

**TO:** **Karen Wickersham, RN**

**FROM:** Brandon Kaukus
UPCI PRC Coordinator, Clinical Research Services

**DATE:** **February 25, 2011**

**RE:** **UPCI 11-016: A Study of Medication-Taking for NSCLC Patients Receiving Oral Targeted Therapy**

The above referenced protocol has received expedited approval by the UPCI Protocol Review Committee (PRC), and can be submitted to the IRB for review. Please submit a copy of this memo along with your protocol when you submit it to the IRB. Any changes made to the study design in the future should be submitted to the committee for review prior to your submission to the IRB. Should you have any questions, do not hesitate to contact me at 623-3376 or email to kaukusbm@upmc.edu.

# APPENDIX B

## UNIVERSITY OF PITTSBURGH

## ORIGINAL INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL LETTER

**University of Pittsburgh**
***Institutional Review Board***

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

## Memorandum

To: Karen Wickersham, BSN, RN

From: Christopher Ryan, PhD, Vice Chair

Date: 6/22/2011

IRB#: PRO11060054

Subject: A Study of Medication-taking for Patients with Non-Small Cell Lung Cancer Receiving Oral Targeted Therapy

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The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:
45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain informed consent to use protected health information to identify potential research subjects.

The IRB has approved the advertisement that was submitted for review as written. As a reminder, any changes to the wording of the approved advertisement would require IRB approval prior to distribution.

This study is supported by the following federal grant application:
F31NR011261 A Study of Medication-Taking for NSCLC Patients Receiving Oral Targeted Therapy

Approval Date: 6/22/2011
Expiration Date: 6/21/2012

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh),

FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

**Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.**

# APPENDIX C

## IRB STUDY RENEWAL LETTER

**University of Pittsburgh**
***Institutional Review Board***

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

**Memorandum**

To: Karen Wickersham, MSN, RN
From: Christopher Ryan, PhD, Vice Chair
Date: 4/25/2012
IRB#: REN12040198 / PRO11060054
Subject: A Study of Medication-taking for Patients with Non-Small Cell Lung Cancer Receiving Oral Targeted Therapy

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Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:
45 CFR 46.110.(7) characteristics/behaviors

Please note the following information:

Approval Date: 4/25/2012
Expiration Date: 4/24/2013

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

**Please be advised that your research study may be audited periodically by the University of Pittsburgh**

# APPENDIX D

## PARTICIPANT INFORMED CONSENT FORM

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: A Study of Medication-Taking for NSCLC Patients Receiving Oral Targeted Therapy

PRINCIPAL INVESTIGATOR: Karen Wickersham, MSN, RN

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Christopher Lindberg, PA II
Hillman Cancer Center
OHA00-Hillman
Pittsburgh, PA 15232
412-235-1020

SOURCE OF SUPPORT: National Institute of Nursing Research
American Cancer Society
Sigma Theta Tau International, Eta Chapter

**Why is this research being done?**

You are being asked to participate in a research study because we would like to explore the process of medication-taking for men and women who are or have received oral targeted therapy for treatment of their non-small cell lung cancer (a type of lung cancer). Medication-taking can be described as a complicated set of activities concerning how you take your medicines. Oral targeted therapies are medicines that act on, or "target", certain sites on or in cancer cells to stop the growth of a tumor. An example of oral targeted therapy is Tarceva® (erlotinib).

The experiences of men and women about their oral targeted therapy, including adherence (the degree to which a person follows the instructions they are given for a prescribed treatment), are not well known. Information learned from this study will add to our understanding about medication-taking related to oral targeted therapy.

**Who is being asked to take part in this research study?**

You are being invited to take part in this research study because you:

- Are a man or woman 18 years of age or older
- Have been diagnosed with non-small cell lung cancer
- Are or have received treatment with a type of oral targeted therapy, called an epidermal growth factor receptor inhibitor (EGFR inhibitor).
- Are able to speak, read, and understand the English language.

Approximately 14-20 men and women are being asked to take part in this study. The research procedures below may take place at the Clinical Research Suites at the University of Pittsburgh, School of Nursing or at the University of Pittsburgh Cancer Institute at your convenience. If you choose, the procedures may also take place at your home, or at another location of your choosing that you consider private and is convenient for you.

**What procedures will be performed for research purposes?**

If you decide to take part in this research study, you will undergo the following procedures that are not part of your standard medical care:

**Screening Procedures:**

Procedures to determine if you are eligible to take part in a research study are called "screening procedures". For this research study, the screening procedures include:

1. Cognitive Functioning Screening: Because decreased cognitive functioning (the ability to maintain attention and remember things) can affect how you take your medications, we will need to assess for cognitive changes by asking you to complete a questionnaire. The questionnaire takes about 5 minutes to complete.

2. Demographic Information: Information about yourself, such as your age, race/ethnicity, religion, occupation, marital status, insurance coverage, and level of education, will be recorded by asking you to complete a questionnaire. The questionnaire takes about 10 minutes to complete. If you choose, we can help you complete this questionnaire by recording your answers to each of the questions.

3. Lung Cancer Information: Information about the type of lung cancer you have, prior treatment (such as chemotherapy or radiation), and current treatment of your cancer will be recorded on a questionnaire. The researcher will obtain this information from your medical record.

It is possible that as a result of these screening procedures, you may not be able to participate in this study. If you are not eligible to participate in the study due to evidence of decreased cognitive functioning, we will refer you to your oncologist for further assessment and workup and your data will be destroyed.

**Interview Procedures:**

If you qualify to take part in this research study, you will be asked to participate in an interview. The interview will take place at the Clinical Research Suites at the University of Pittsburgh, School of Nursing or at the University of Pittsburgh Cancer Institute at your convenience. If you choose, the interview may also take place at your home, or at another location of your choosing that you consider private and is convenient for you.

The interview will take about 45 minutes to complete.

The interview will be conducted by a nurse researcher and will be digitally (audio) recorded so that there is an accurate record of what is discussed. The tapes will only be reviewed by members of the research team, who will transcribe and analyze them. All transcripts, field notes and digital recorders will be kept in a locked drawer for a period of at least 7 years.

During the interview, you will be asked questions about your experiences taking oral targeted therapy; for example, you may be asked about why you began taking your therapy, how you take it on a typical day, what you find difficult or challenging about taking the therapy, etc.

In addition, you will be asked for your permission for the researcher to photograph any objects or "artifacts" which are important to you in taking your oral targeted therapy. Some examples of these objects may include a medication diary or notebook, storage containers, or other handcrafted objects. Pictures of these objects are important in helping us understand the total process of medication-taking and how you take your oral targeted therapy. The choice of the object to photograph will be decided between yourself and the researcher. If you agree, the photograph will be taken during the interview.

**Follow-Up Interview Procedures:**

You may be asked to participate in another interview after you have finished at least 1-2 months of oral targeted therapy. If you agree to another interview, the process will be the same as the one described above. During the interview, you will be asked similar questions about your experiences taking oral targeted therapy. This interview will also take about 45 minutes to complete.

**What are the possible risks, side effects, and discomforts of this research study?**

**Risks of Completion of the Questionnaires:**

It is possible that while you are completing of some of the screening questionnaires that you may become upset or fatigued. To lessen any fatigue, which may occur, you will be offered breaks while you complete the questionnaires.

**Risks of Participating in the Interview:**

It is possible that you may experience some fatigue or emotional discomfort as a result of the interview process. To lessen any fatigue, which may occur, you will be offered breaks during the interview.

Should you tell the researcher that you are experiencing any emotional discomfort, the investigator will immediately address and will offer to make a phone call to your oncologist, if needed. In addition, if you are in need of psychological counseling or psychiatric referral, we will provide you with referral information. If at any time you feel the need to stop the interview, the researcher will stop the interview and offer to resume it at a later date. You may choose to stop the interview at any time for any reason, if needed.

**Risk of Breach of Confidentiality:**

There is a possibility of the risk of breach of confidentiality of protected health information. The research staff will take all necessary steps to ensure that this does not happen, including but not limited to removing your identifying information from reports, keeping your records in a locked file room, and using passwords for computer files.

**Risk of Photographs**

Photographing objects related to your medication-taking process will not impose additional risks. The researcher will make sure that there is nothing in the image of the object that would identify you, or that would identify you as a patient with non-small cell lung cancer, or any cancer.

We wish to use photographs of the objects taken during your interviews for the purpose of recording and describing this project. These images may appear in academic publications, presentations given at academic conferences, or on the Internet. These photographs may also appear in newspapers or newsletters. You will be asked to sign a separate consent form (release) giving your permission for publication of the photographs. You may participate in the research study, without being recorded, even if you do not sign this form.

**What are possible benefits from taking part in this study?**

You will likely receive no direct benefit from taking part in this interview. It is our hope that information from this research study may benefit patients with lung cancer or other types of cancer in the future.

**Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?**

Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study (i.e., the screening procedures, the interview, or follow-up interview described above). You will be charged, in the standard manner, for any procedures performed for your routine medical care.

**Will I be paid if I take part in this research study?**

You will be provided a stipend for participating in this research study. You will receive $10 after completion of each interview.

**Who will pay if I am injured as a result of taking part in this study?**

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

**Who will know about my participation in this research study?**

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

**Will this research study involve the use or disclosure of my identifiable medical information?**

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., physician office) records. The information that will be recorded will be limited to your age, race, employment, number of years of education that you have completed and information about your lung cancer diagnosis and treatment.

**Who will have access to identifiable information related to my participation in this research study?**

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

**For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?**

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of six (6) years after final reporting or publication of a project.

**May I have access to my medical information that results from my participation in this research study?**

In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

**Is my participation in this research study voluntary?**

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for

the purposes described above, you will not be allowed to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

**May I withdraw, at a future date, my consent for participation in this research study?**

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

**If I agree to take part in this research study, can I be removed from the study without my consent?**

It is possible that you may be removed from the research study by the researchers if there is a change in your lung cancer treatment or as a result of the screening procedures. If you are excluded from the study due to evidence of cognitive impairment, you will be referred to your oncologist for further assessment and workup. You may withdraw from the study at any time, if you wish.

**Might I be contacted after I have completed my participation in this study?**

You may be contacted after you have completed this study if there is a need for more information from you for this study, or if the researchers have other studies in which you may be interested in participating.

**********

VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____ _____ _____

Participant's Signature Printed Name of Participant Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date

# APPENDIX E

# PARTICIPANT CONSENT ADDENDUM

**ADDENDUM**

**CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY**

**TITLE:** A Study of Medication-Taking for NSCLC Patients Receiving Oral Targeted Therapy

**PRINCIPAL INVESTIGATOR:** Karen Wickersham, MSN, RN
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Telephone: 412-721-5899

**CO-INVESTIGATORS:**

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412-235-1020

Christopher Lindberg, PA II
Hillman Cancer Center
OHA00-Hillman
Pittsburgh, PA 15232
412-235-1020

**ADDITIONAL RESEARCH PROCEDURE:**

You are currently a participant in a research study that explores the process of medication-taking for men and women who are receiving or have received oral targeted therapy for treatment of their non-small cell lung cancer (a type of lung cancer). Medication-taking can be described as a complicated set of activities concerning how individuals take their medicines. Oral targeted therapies are medicines that act on, or "target", certain sites on or in cancer cells to stop the growth of a tumor. An example of oral targeted therapy is Tarceva® (erlotinib).

In addition to the interviews that you have or are completing, we would like to ask for your permission for the researcher to photograph any objects or "artifacts" which are important to you in taking your oral targeted therapy. Some examples of these objects may include a medication diary or notebook, storage containers, or other handcrafted objects. Pictures of these objects are important in helping us understand the total process of medication-taking and how you take your oral targeted therapy. The choice of the object to photograph will be decided between yourself and the researcher. If you agree, the photograph will be taken during the interview.

Risk of Photographs

Photographing objects related to your medication-taking process will not impose additional risks. The researcher will make sure that there is nothing in the image of the object that would identify you, or that would identify you as a patient with non-small cell lung cancer, or any cancer.

We wish to use photographs of the objects taken during your interviews for the purpose of recording and describing this project. These images may appear in academic publications, presentations given at academic conferences, or on the Internet. These photographs may also appear in newspapers or newsletters. You will be asked to sign a separate consent (release) form giving your permission for publication of the photographs. You may participate in the research study, without being recorded, even if you do not sign this form.

***Might I be contacted after I have completed my participation in this study?***

You may be contacted after you have completed this study if there is a need for more information from you for this study, or if the researchers have other studies in which you may be interested in participating**.**

**Allowing us to photograph these objects is entirely voluntary. Your refusal will not affect your participation in NSCLC and Medication-Taking Study.**

**RIGHT TO WITHDRAW**

You understand that you can withdraw from this research study at any time. Your other care and benefits will be the same whether you participate in this research study or not. You also understand that you may be removed from this research study by the investigators in the event of a significant risk to your health.

**********

**VOLUNTARY CONSENT**

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

| _____ | _____ | _____ |
|---|---|---|
| Participant's Signature | Printed Name of Participant | Date |

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

| _____ | _____ |
|---|---|
| Printed Name of Person Obtaining Consent | Role in Research Study |

| _____ | _____ |
|---|---|
| Signature of Person Obtaining Consent | Date |

# APPENDIX F

## INTERVIEW GUIDE

We are taping the conversation with your permission because I want to be sure not to miss or leave anything out that you are telling me. Is this ok? I may also take some notes as we go along.

Introduction: I am interested in understanding/learning about your experience in taking the anti-cancer medication (name of EGFR inhibitor [e.g. Tarceva®])

First, I would like you to tell me about your (name of medicine),

(Probes) Why and when did you start on the medication?

How did you decide to start taking the medication?

What is it like to be on that kind of treatment?

How does the medication make you feel?

How is this different from your previous treatment?

What were you told about the medication?

Tell me about how you take (name of medicine), during a typical day.

(Probes) What kind of strategies do you use to help you take them?

How do you decide <u>when</u> to take them?

What do you find difficult or challenging (use their word) (barriers) about taking this medication?

What would be your "deal breaker"?

Patients sometimes miss doses or find the medication difficult to take at the same time each day. How is that for you?

(Probes) Can you tell me more about that?

What happens when you miss a dose?

What happens when a dose is late?

Some people don't realize that they forget doses. Does that ever happen for you? Tell me more.

(Probes) What was your reaction when you realized you forgot a dose?

Were there unexpected, non-routine things?

What were you told to do if you missed a dose?

What would make it easier for you to take your medication at the same time each day?

What would have to change to make taking your medication easier?

Do you experience any side effects that interfere with taking your medicine? If so, how do you manage them in terms of your medication (i.e. dose reductions?)?

For those who had chemotherapy, how is the oral medication different from chemo/other treatments?

What people in your life are helpful to you in taking the medication?

(Probes) Can you tell me more about that? In what ways does he/she help?

How have health care providers helped you in taking the medication?

Field Notes:

Environment (lighting, noise, temperature):

Positioning

Body Language

Appearance

Eye contact

Tone

Emotions

Interruptions

Impressions (Informative?  New issues raised?)

# APPENDIX G

## INTERVIEW CHECKLIST

____ Create participant folder on hard drive

____ Enter interview information onto participant tracking spreadsheet

**Pre-Interview, 1 day before:**

____ Call to confirm interview

____ 2 informed consent forms:

- 1 for signature to bring back and file,
- 1 for participant,
- Participant to initial all pages.

____ Print interview guide and field notes

____ Print participant payment form

____ Print WePay activation form

____ $10 stipend (WePay Card)

____ Set up transcript template

**Interview (Day of):**

____ Bring:

- Digital tape recorder and bag with back-up recorder, batteries, USB.
- Directions to location of interview (hard copy and GPS).
- Cell phone
    - 2 informed consent forms
    - Participant payment form

- $10 stipend (WePay Card)
- WePay Activation Form

____ Informed consent process

____ MMSE

____ SDG Form

____ Confirmation of eligibility

**Immediately Post-Interview:**

____ Check tape recorder

____ Write impressions

**Post-Interview, within 24 hours:**

___ Load WePay card

___ File:

- Informed consent form
- Participant payment form
- Interview checklist
- Interview guide with field notes

____ Download interview

____ Transfer interview and transcript template to Dropbox

____ Enter completion of interview onto tracking sheet

# APPENDIX H

# PATIENT REFERRAL PAMPHLET

**Crisis and Suicide Hotline**
412-820-HELP or 1-800-SUICIDE
24 hours day/7 days week

The Crisis and Suicide Hotline offers immediate emotional support by telephone volunteers trained to help people of all ages who may be suicidal, in emotional distress or in need of reassurance. Services are free, confidential, and anonymous.

**Reassurance for Seniors**
412-820-0100

Reassurance for Seniors provides a free, friendly, daily (or weekly) call to senior adults, both for friendly conversation and for the primary purpose of confirming their health and safety. A trained volunteer is assigned to a senior and makes the call at a mutually agreed upon time.

**UPMC Cancer Centers Behavioral Medicine Services**
Phone: 412-623-5888 (for all locations)
Magee-Women's Hospital
Hillman Cancer Center
UPMC Passavant

UPMC Cancer Centers Behavioral Medicine provides a range of supportive care and psychological services to patients and families. The diagnosis and treatment of cancer may be stressful and many experience distress and poorer quality of life than they had previously. Some want to take a more active role in prevention of recurrent or new cancers once treatments are completed. A number of patients and family members may experience transient depression, anxiety, or sleep loss and some experience persistent pain or fatigue.

Behavioral Medicine has provided for cancer patients and their families with:

Coping skills ●training relaxation ●training pain management ●stress management ●general psychological counseling and treatment support groups ●exercise programs ●behavioral treatments that decrease side-effects of treatments and improve quality of life

**UPMC Cancer Centers Social Work Services**
Magee Women's Hospital: 412-641-1178
For other UPMC Cancer Centers, call your local center for referral.

Social work services at UPMC Cancer Centers are provided by oncology social workers and include individual, family and group counseling, education, advocacy, discharge planning, case management and program development. These services are designed to maximize the patient's utilization of the health care system, foster coping and access community resources to support optimal functioning.

The focus of care may relate to the following:

Adjusting to the emotional impact of a cancer diagnosis ● realigning family roles ●coping with chronic illness ●stress management ●communicating with children about cancer ●adjusting to changes in self-image and sexuality ●learning to negotiate the complexities of the health care system ● managing financial and insurance concerns ●returning to the workplace ●planning for care after hospitalization ●coping with bereavement

Oncology social workers also offer a number of support/educational groups to patients with cancer and their family members.

**Western Psychiatric Institute and Clinic**
3811 O'Hara Street
Pittsburgh, PA 15213-2593

**Emergency and Crisis Intervention Services: 412-624-2000**

The Diagnostic Evaluation Center (DEC) provides 24 hour, seven day a week emergency and crisis intervention services, including psychiatric emergency evaluations, walk-in crisis therapy, referral to outpatient providers, and facilitation of inpatient admissions. The mission is to provide comprehensive mental health and substance abuse evaluations and referral to appropriate services for people of all ages, in various states of crisis.

Consumers can access the DEC directly, or be referred by an outside source for evaluation of mental health or substance abuse problems. Consumers meet with a team that includes a nurse, clinician, and doctor, all specializing in the field of psychiatry. The team then works with the individual and family to determine the best options for treatment.

**Outpatient Services:**

**412-624-1000**

Outpatient programs at Bellefield Towers treat a wide variety of conditions including depression, anxiety, compulsive disorders and phobias.

# APPENDIX I

## SOCIODEMOGRAPHIC AND NSCLC HISTORY CASE REPORT FORM

*Note: To be abstracted from the medical chart or administered verbally (adapting language/clarifying where appropriate). This information will be entered directly from this form into an SPSS database.*

**Demographics**

Age in years:

Gender:

Occupation:

Marital Status (married/single/divorced/widowed):

Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other):

Ethnicity (Hispanic or Latino, Not Hispanic or Latino):

Religion (self-identified):

Level of education (in years):

Insurance coverage:

**NSCLC History**

NSCLC type:

Date diagnosed:

Stage at diagnosis:

EGFR mutation (yes/no):

Radiation Therapy:

Type of radiation (1):

Date began:

Date ended:

Type of radiation (2):

Date began:

Date ended:

Chemotherapy:

- Drug Name #1:

  Number of cycles:

  Dose/route

- Drug Name #2:

  Number of cycles:

  Dose/route

- Drug Name #3:

  Number of cycles:

  Dose/route

- Drug Name #4:

  Number of cycles:

  Dose/route

- Drug Name #5:

  Number of cycles:

  Dose/route

Oral Targeted Therapy:

Name:

Dose/Route/Frequency:

Date started:

Date stopped:

Instructions given for taking medication:

Discontinued? (yes/no)

Reason discontinued and when?

Dose reduced?

Reason and when?

Other therapy (e.g. bevacizumab):

Name:

Dose/Route/Frequency:

# APPENDIX J

# ADVERTISEMENT

Karen Wickersham, MSN, RN, University of Pittsburgh, School of Nursing is recruiting men and women with a diagnosis of non-small cell lung cancer to participate in a research study funded by the National Institute of Nursing Research and the American Cancer Society.

The purpose of the study is to explore the process of medication-taking (how people take their medications) for men and women who are or have received oral targeted therapy for treatment of their non-small cell lung cancer.

The study consists of 1 to 2 interviews at this site, or at a location that is convenient for you and gives you privacy (such as your home). Each visit will take about 1 to 1 ½ hours. You will be paid for each interview.

**Study visits include:**

- Completing a questionnaire concerning cognitive function (the ability to maintain attention and remember things).
- Answering questions about yourself such as your age and place of employment.

**To participate, you must:**

- Be 18 years of age or older (both men and women may participate).
- Have been diagnosed with non-small cell lung cancer.
- Are or have received treatment with a type of oral targeted therapy, called an epidermal growth factor receptor inhibitor (EGFR inhibitor) (e.g. Tarceva®).
- Are able to speak, read, and understand the English language.

## Participation is voluntary and completely confidential.

ASK YOUR DOCTOR OR NURSE FOR MORE INFORMATION ABOUT THIS STUDY OR CALL: 412-721-5899



NSCLC and Medication-Taking
Karen Wickersham
Study number: 412-721-5899

NSCLC and Medication-Taking
Karen Wickersham
Study number: 412-721-5899
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NSCLC and Medication-Taking
Karen Wickersham
Study number: 412-721-5899

**BIBLIOGRAPHY**


Abou-Jawde, R., Choueiri, T., Alemany, C., & Mekhail, T. (2003). An overview of targeted treatments in cancer. *Clinical Therapeutics, 25*(8), 2121-2137. doi: 10.1016/S0149-2918(03)80209-6

Aisner, J. (2007). Overview of the changing paradigm in cancer treatment: Oral chemotherapy. *American Journal of Health-System Pharmacists, 64*(Supp 5), S4-S7. doi: 10.2146/ajhp070035

Amador, M. L., Oppenheimer, D., Perea, S., Maitra, A., Cusatis, G., Iacobuzio-Donahue, C., …Hidalgo, M. (2004). An epidermal growth factor receptor intron 1 polymorphism mediates response to epidermal growth factor receptor inhibitors. *Cancer Research, 64*(24), 9139–9143. doi:10.1158/0008-5472.CAN-04-1036

American Cancer Society. (2011a). Lung cancer key statistics. Retrieved on April 4, 2011 at: http://www.cancer.org/Cancer/LungCancer-Non-SmallCell/DetailedGuide/non-small-cell-lung-cancer-key-statistics.

The ATAC (Arimidex, Tamoxifen, Alone or in Combination). (2002). Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *Lancet, 359*, 2131-2139. doi: 10.1016/S0140-6736(02)09088-8

Atkins, L. & Fallowfield, L. (2006). Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *European Journal of Cancer, 42*(14), 2271-2276. doi: 110.1016/j.ejca/2006.03.004

Bach, P. B. (2009). Limits on one's ability to control rising spending on cancer drugs. *New England Journal of Medicine, 360*, 626-633. doi: 10.1056/NEJMhpr0807774

Bacjar, J. (2006). Task analysis of patients' medication-taking practice and the role of making sense: A grounded theory study. *Research in Social and Administrative Pharmacy, 2*, 59-82. doi: 10.1016/j.sapharm.2005.12.005

Barron, T. I., Connolly, R., Bennett, K., Feely, J., & Kennedy, M. J. (2007). Early discontinuation of tamoxifen: A lesson for oncologists. *Cancer, 109*, 832-839. doi: 10.1002/cncr.22485

Bartel, S. B. (2007). Safe practices and financial considerations in using oral chemotherapy agents. *American Journal of Health-System Pharmacy, 64*(9, Suppl 5), S8-S14. doi: 10.2146/ajhp070036

Bedell, C. H. (2003). A changing paradigm for cancer treatment: The advent of new oral chemotherapy agents. *Clinical Journal of Oncology Nursing, 7*(6 Suppl), 5-9. doi: 10.1188/03.CJON.S6.5-9

Bezjak, A., Tu, D., Seymour, L., Clark, G., Trajkovic, A., Zukin, M., … Shepherd, F. A. (2006). Symptom improvement in lung cancer patients treated with erlotinib: Quality of life analysis of the national cancer institute of Canada clinical trials group study BR.21. *Journal of Clinical Oncology, 24*(24), 3831-3837. doi: 10.1200/jco.2006.05.8073

Bonomi, P. D. (2003). Epidermal growth factor receptor-targeted therapy and symptom improvement in non-small cell lung cancer. *American Journal of Health-System Pharmacists, 60*(Suppl 9), S16-S21.

Boone, S. L., Rademaker, A., Liu, D., Pfeiffer, C., Mauro, D. J., & Lacouture, M. E. (2007). Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology, 72*(3-4), 152-159.

Bunn, P. & Thatcher, N. (2008). Introduction. *The Oncologist, 13*(suppl 1), 1-4. doi: 10.1016/theoncologist.13-S1-1

Busam, K. J., Capodieci, P., Motzer, R., Kiehn, T., Phelan, D., & Halpern, A. C. (2001). Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *British Journal of Dermatology, 144*, 1169-76.

Butler, J. A., Peveler, R. C., Roderick, P., Horne, R., & Mason, J. C. (2004). Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. *Transplantation Forum, 77* (5), 786-789. doi: 10.1097/01.TP.0000110412.200S0.36

The Centers for Disease Control and Prevention. (2007). *Morbidity and mortality weekly report*, "Cigarette smoking among adults-United States, 2006." November 9, 2007/56(4), 1157-1161.

Chambers, J. A., O'Carroll, R. E., Hamilton, B., Whittaker, J., Johnston, M., Sudlow, C., & Martin, D. (2011). Adherence to medication in stroke survivors: A qualitative comparison of low and high adherers. *British Journal of Health Psychology, 16*(3), 592-609. doi: 10.1348/2044-8287.002000

Chen, C. -H., Wu, J. -R., Yen, M., & Chen, Z. -C. (2007). A model of medication-taking behavior in elderly individuals with chronic disease. *Journal of Cardiovascular Nursing, 22*(5), 359-365.

Choo, P. W., Rand, C. S., Inui, T. S., Lee, M. -L. T., Cain, E., Cordeiro-Breault, M., …Platt, R. (1999). Validation of patient reports, automated pharmacy records, and pill counts with

electronic monitoring of adherence to antihypertensive therapy. *Medical Care, 37*(9), 846-857.

Clatworthy, J., Bowskill, R., Rank, T., Parham, R., & Horne, R. (2007). Adherence to medication in bipolar disorder: A qualitative study exploring the role of patients' belief about the condition and its treatment. Bipolar Disorders: An International Journal of Psychiatry and Neurosciences, 9(6), 656-664. doi: 10.1111/j.1399-5618.2007.00434.x

Cobb, A. K. & Hagemaster, J. N. (1987). Ten criteria for evaluating qualitative research proposals. *Journal of Nursing Education, 26*(4), 138-143.

Conwell, L. J., Esposito, D., Colby, M., Ball, D, Meadows, E. S., & Marciniak, M. (2011). Promising therapies, prohibitive costs: A qualitative assessment of the effects of the Medicare Part D doughnut hole on access to costly cancer medications. *Community Oncology, 8*(3), 111-117.

Coombes, R. C., Hall, E., Gibson, L. J., Paridaens, R., Jassem, J., Delozier, T., …van de Velde C. (2004). A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *New England Journal of Medicine, 350*, 1081-1092.

Corbin, J. & Strauss, A. (2008). *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory* (3rd ed.). Los Angeles, CA: Sage Publications.

Cutliffe, J. R. (2000). Methodological issues in grounded theory. *Journal of Advanced Nursing, 31*(6), 1476-1484.

Darkow, T., Henk, H. J., Thomas, S. K., Feng, W., Baladi, J. F., Goldberg, G. A., …Cortes, J. (2007). Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukemia. *Pharmacoeconomics, 25*, 481-496.

Davies, M., Houlihan, N. G., & Joyce, M. (2004). Lung cancer control. In: Houlihan NG, ed. *Site Specific Cancer Series: Lung Cancer* (p. 17-34). Pittsburgh, PA: Oncology Nursing Society.

Decker, V., Spoelstra, S., Miezo, E., Bremer, R., You, C., Given, C., & Given, B. (2009). A pilot study of an automated voice response system and nursing intervention to monitor adherence to oral chemotherapy agents. *Cancer Nursing, 32*(6), E20-E-29.

De Geest, S., Shafer-Keeler, P., Denhaerynck, K., Thannberger, N., Kofer, S., Bock, A., … Steiger, J. (2006). Supporting medication adherence in renal transplantation in (SMART): a pilot RCT to improve adherence to immunosuppressive regimens. *Clinical Transplant, 20*, 259-368. doi: 10.1111/j.1399-0012.2006.00493.x

Demissie, S., Silliman, R. A., & Lash, T. L. (2001). Adjuvant tamoxifen: Predictors of use, side effects and discontinuation in older women. *Journal of Clinical Oncology, 19*, 322-328.

Denois, V. R., Poirson, J., Nourissat, A., Jacquin, J. –P., Guastalla, J. P., & Chauvin, F. (2011). Adherence with oral chemotherapy: results from a qualitative study of the behavior and representations of patients and oncologists. *European Journal of Cancer Care, 20,* 520-527.

DiMatteo, M. (2004). Evidence-based strategies to foster adherence and improve patient outcomes. *Journal of the American Academy of Physician Assistants, 17*, 18-21.

Dowell, J., & Hudson, H. (1997). A qualitative study of medication-taking behaviour in primary care. *Family Practice, 14*(5), 369-375.

Druker, B. J., Sawyers, C. L., Kantarjian, H., Resta, D. J., Reese, S. F., Ford, J. M., …Talpaz M. (2001). Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *New England Journal of Medicine, 344*, 1038-1042.

Dunbar-Jacob, J., Erlen, J. A., Schlenk, E. A., Ryan, C. M., Sereika, S. M., & Doswell, W. M. (2000). Adherence in chronic disease. *Annual Review of Nursing Research, 18*, 48-90.

Eames, T., Kroth, J., Flaig, M. J., Ruzicka, T., & Wollenberg, A. (2010). Perifollicular xanthomas associated with epidermal growth factor receptor inhibitor therapy. *Acta Dermato-Venereologica, 90*(2), 202-203. doi: 10.2340/00015555-0792

Edwards, B. K., Howe, H. L., Ries, L. A., Thun, M. J., Rosenberg, H. M., Yancik, R., …Feigal, E. G. (2002). Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. *Cancer, 94*, 2766-2792. doi: 10.1002/cncr.10593

Edwards, B. K., Brown, M. I., Wingo, P. A., Howe, H. L, Ward, E., Ries, L. A. G., … Pickle, L. W. (2005). Annual report to the nation on the status of cancer, 1975-2005, featuring population-based trends in cancer treatment. *Journal of the National Cancer Institute, 97*, 1407-1427. doi: 10.1093/jnei/dji289

Elliott, R. A. (2006). Problems with medication use in the elderly: an Australian perspective. *Journal of Pharmacy Practice Research, 36*, 58-66.

Erlen, J. A. & Mellors, M. P. (1999). Adherence to combination therapy in persons living with HIV: Balancing the hardships and the blessings. *Journal of the Association of Nurses in AIDS Care, 10*(4), 75-84. doi: 10.1016/S1055-3290(06)603129

Erlen, J., Sereika, S. M., Cook, R. L., & Hunt, S. C. (2002). Adherence to antiretroviral therapy among women with HIV infection. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 31*(4), 470-477. doi: 10.1111/j.1552-6909.2002.tb00070.x

Erlen, J. A. & Happ, M. (2006). Patients with Alzheimer's disease who live at home: The challenge of medication-taking. Podium presentation presented at the18th Scientific Sessions of the Eastern Nursing Research Society, Philadelphia, PA.

Ersek, M., Krapbill, B. M., & Du Pen, A. (1999). Factors hindering patients' use of medication for cancer pain. *Cancer Practice, 7*(5), 26-232.

Evangelista, L. S., Doering, L. V., Dracept, K., Westlake, C., Hamilton, M., & Fonarow, G. C. (2003). Compliance behaviors of elderly patients with advanced heart failure. *Journal of Cardiovascular Nursing, 18*, 197-208.

Fink, A. K., Gurwitz, J., Rakowski, W., Guadagnoli, E., & Silliman, R. A. (2004). Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. *Journal of Clinical Oncology, 22*(16), 3309-3315.doi: 10.1200/JCO.2004.11.064

Finkelstein, D. M., Ettinger, D. S., & Ruckdeschel, J. C. (1986). Long-term survivors in metastatic non-small cell lung cancer: An Eastern Cooperative Oncology Group study. *Journal of Clinical Oncology, 4*(5), 702-709.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.

Fukuoka, M., Yano, S., Giaccone, G., Tamura, T., Nakagawa, K., Douillard, J. –Y., …Baselga, J. (2003). Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non–small-cell lung cancer. *Journal of Clinical Oncology, 21*, 2237– 2246.

Ganesan, P., Sagar, T. G., Dubashi, B., Rajendranath, R., Kannan, K., Cyriac, S., & Nandennavar, M. (2011). Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. *American Journal of Hematology, 86*, 471-474. doi: 10.1002/ajh.22019

Ganti, A. K., deShazo, M., Weir, A. B., & Hurria, A. (2012). Treatment of non-small cell lung cancer in the older patient. *Journal of the National Comprehensive Cancer Network, 10*(2), 230-239.

Gebbia, V., Bellavia, M., Russo, P., Banna, G. L., Ferraù, F., Tralongo, P., & Borsellino, N. (2011). Implementation of adherence to erlotinib by a treatment-monitoring program. *Journal of Clinical Oncology, 29*(sup; abstr 7611).

Genentech. (2008). Non-small cell lung cancer. Genentech Web site. http://www.gene.com/gene/products/education/oncology/lungcancerfact.html. Accessed May 23, 2008.

Glaser, B. G. & Strauss, A. L. (1967). T*he Discovery of grounded theory: Strategies for qualitative research.* Chicago, IL: Adline Publishing Company.

Goss, P. E., Ingle, J. N., & Martino, S. (2003). A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *New England Journal of Medicine, 349*, 1793-1802.

Gray, J. (2006). Becoming adherent: Experiences of persons living with HIV/AIDS. *Journal of the Association of Nurses in AIDS Care, 17*(3), 47-54. doi: 10.1016/j/jana.2006.03.004

Gray, S. L., Mahoney, J. E., & Blough, D. K. (2001). Medication adherence in elderly patients receiving home health services following hospital discharge. *Annals of Pharmacotherapy, 35*, 539-545.

Gridelli, C., Bareschino, M. A., Schettino, C., Rossi, A., Maione, P., & Ciardiello, F. (2007). Erlotinib in non-small cell lung cancer treatment: Current status and future development. *The Oncologist, 12*, 840-849. doi: 10.1634/theoncologist.12-7-840.

Grunfeld, E. A., Hunter, M. S., Sikka, P., & Mittal, S. (2005). Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Education and Counseling, 59*, 97-102. doi: 10.1016/j/pec.2004.10.005

Halpern, R., Barghout, V., Mody-Patel, N., & Williams, D. (2008). Relationship between compliance, costs, hospitalizations for CML and GIST patients using imatinib mesylate [abstract]. *Journal of Clinical Oncology, 26*(5S), Abstract 6598.

Harari, P. (2004). Epidermal growth factor receptor inhibition strategies in oncology. *Endocrine-Related Cancer, 11*, 689-708. doi: 10.1677/erc.1.00600

Hayes, D. N., Monti, S., Parmigiani, G., Gilks, C. G., Naoki, K., Battacharjee, A., …Meyerson, M. (2006). Gene expression profiling reveals reproducible human lung adenocarcinoma subtypes in multiple independent patient cohorts. *Journal of Clinical Oncology, 24*, 5079-5090. doi: 10.1200/JCO.2005.05.1748

Haynes, R., Ackloo, E., Sahota, N., McDonald, H., & Yao, X. (2008). Interventions for enhancing medication adherence (review). *The Cochrane Collaboration, 2*, 1-127.

Hehlmann, R., Berger, U., & Hochhaus A. (2005). Chronic myeloid leukemia: a model for oncology. *Annals of Hematology, 84*, 487-497.

Herbst, R. S. & Shin, D. M. (2002). Monoclonal antibodies to target epidermal growth factor-positive tumors: a new paradigm for cancer therapy. *Cancer, 95*, 1593-1611.

Hon, A. (2012). Factors influencing the adherence of antipsychotic medications (Apripazole) in first-episode psychosis: Findings from a grounded theory study. *Journal of Psychiatric and Mental Health Nursing, 19*, 354-361. doi: 10.1111/j.1365-2850.2012.01898.x

Horn, L., Visbal, A., & Leighl, N. B. (2007). Docetaxel in non-small cell lung cancer: Impact on quality of life and pharmacoeconomics. *Drugs & Aging, 24*(5), 411-428.

Horio, Y., Takahashi, T., Kurioshi, T., Hibi, K., Suyama, M., Niimi, T., …Takahashi, T. (1993). Prognostic significance of p53 mutations and 3p deletions in primary resected non-small cell lung cancer. *Cancer Research, 53*, 1-4.

Ibrahim, A. R., Eliasson, L., Apperley, J. F., Milojkovic, D., Bua, M., Szydlo, R., …Marin, D. (2011). Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood,* 117(14), 3733-3736. doi: 10.1182/blood-2010-10-309807.

Johnson, M. J., Williams, M., & Marshall, E. S. (1999). Adherent and nonadherent medication-taking in elderly hypertensive patients. *Clinical Nursing Research, 8*, 318-335. doi: 10.1177/10547739922158331

Jones, S. (2003). Pharmacy practice issues with targeted therapy for lung cancer. *American Journal of Health-System Pharmacists, 60*(suppl 9), S11-S15.

Jorgensen, T., Johansson, S., Kennerfalk, A., Wallander, M. A., & Svardsudd, K. (2001). Prescription drug use, diagnoses, and healthcare utilization among the elderly. *Annals of Pharmacotherapy, 35*, 1004-1009.

Joshi, S. S., Ortiz, S., Witherspoon, J. N., Rademaker, A., West, D. P., Anderson, R., …Lacouture, M. E. (2010). Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. *Cancer, 116*, 3916–3923. doi: 10.1002/cncr.25090

Kahn, K. L., Schneider, E. C., Malin, J. L., Adams, J. L., & Epstein, A. M. (2007). Patient centered experiences in breast cancer: Predicting long-term adherence to tamoxifen use. *Medical Care*, 45, 431-439.

Kantarjian, H., Sawyers, C., Hochhaus, A., Guilhot, F., Schiffer, C., Gambacorti-Passerini, C., …Druker, B. International STI571 CML Study Group. (2002). Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *New England Journal of Medicine, 346*, 645-652. [Erratum in: *New England Journal of Medicine*, 2002, *346*, 1923.]

Kingsnorth, D. & Wilkinson, S. (1996). Patient compliance with medication regimens after discharge from palliative care. *International Journal of Palliative Care Nursing, 2*(3), 114-148.

Kris, M. G, Natale, R. B., Herbst, R. S ., Lynch, T. J., Prager, D., Belani, C. P., …Kay, A. C. (2003). Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. *Journal of the American Medical Association, 290*, 2149-2158.

Lababede, O., Meziane, M., & Rice, T. (2011). Seventh edition of the cancer staging manual and stage grouping of lung cancer: Quick reference guide and diagrams. *Chest, 138*, 183-189. doi: 10.1278/chest.10-1099.

Landier, W., Hughes, C. B., Calvillo, E. R., Anderson, N. L. R., Briseno-Toomey, D., Dominguez, L., …Bhatia, S. (2011). A grounded theory of the process of adherence to oral chemotherapy in Hispanic and Caucasian children and adolescents with acute

lymphoblastic leukemia. *Journal of Pediatric Oncology Nursing,* 28(4), 203-223. doi: 10.1177/1043454211409582

Lash, T. L, & Fox, M. P., Westrup, J. L., Fink, A. K., & Silliman, R. A. (2006). Adherence to tamoxifen over the five-year course. *British Cancer Research and Treatment, 99,* 215-220. doi: 10.1007/s10549-006-9193-0

Lash, T. L., Cronin-Fenton, D., Ahern, T. P., Rosenberg, C. L., Lunetta, K. L., …Hamilton-Dutoit, S (2011). CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. *Journal of the National Cancer Institute, 103,* 489–500. doi: 10.1093/jnci/djr010

Lebovits, A. H., Strain, J. J., Schleifer, S. J., Tanaka, J. S., Bhardwaj, S., & Messe, M.R. (1990). Patient noncompliance with self-administered chemotherapy. *Cancer, 65,* 7-22.

Ledlie, S. W. (1999). Diagnosis disclosure by family caregivers to children who have perinatally acquired HIV disease: when the time comes. *Nursing Research, 48*(3), 141-146.

Lee, C., Nicholson, R., Souhami, M., Slevin, M., Hall, M., & Deshmukh, A. (1993). Patient compliance with prolonged low-dose oral etoposide for small cell lung cancer. *British Journal of Cancer, 67,* 630-634.

Lehane, E., McCarthy, G., Collender, V., & Deasy, A. (2008). Medication-taking for coronary artery disease patients - patients' perspectives. *European Journal of Cardiovascular Nursing, 7*(2), 133-139.

Lewis, M., Colbert, A., Erlen, J., & Meyers, M. (2006). A qualitative study of persons who are 100% adherent to antiretroviral therapy. *AIDS Care, 18* (2), 140-148. doi: 10.1080/09540120500161835

Lima, J. J., Thomason, D. B., Mohamed, M. H., Eberle, L. V., Self, T. H., & Johnson, J. A. (1999). Impact of genetic polymorphisms of the beta2-adrenergic receptor on albuterol bronchodilator pharmacodynamics. *Clinical Pharmacology & Therapeutics, 65,* 519–525.

Linjakumpu, T., Hartikainen, S., Klaukka, T., Veijola, J., Kivela, S. -L., & Isoaho, R. (2002). Use of medications and polypharmacy are increasing among the elderly. *Journal of Clinical Epidemiology, 55,* 809-817. doi: 10.1016/S0895-4356(02)00411-0

Love, R. R., Cameron, L., Connell, B. L., & Leventhal, H. (1991). Symptoms associated with tamoxifen treatment in postmenopausal women. *Archives of Internal Medicine, 151*(9), 1842-1847.

Lynch, T. J., Bell, D. W., Sordella, R., Gurubhadavatula, S., Okimoto, R. A., Brannigan, B. W., …Huber, D. A. (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. *New England Journal of Medicine, 350,* 2129-2139.

Macintosh, P. W., Pond, G. R., Pond, B. J., Leung, V., & Siu, L. L. (2007). A comparison of patient adherence and preference of packaging method for oral anticancer agents using conventional pill bottles versus daily pill boxes. *European Journal of Cancer Care, 16,* 380-386. doi: 10.1111/j.1365-2354-2006.00758.x

Maione, P., Rossi, A., Sacco, P. C., Bareschino, M. A., Schettino, C., & Gridelli, C. (2010). Advances in chemotherapy in advanced non-small cell lung cancer. *Expert Opinion on Pharmacotherapy, 11*(18), 2997-3007.

Mazzeo, F., Duck, L., Joosens, E., Dirix, L., Focan, C., Forget, F., …De Greve, J. (2011). Nonadherence to imatinib treatment in patients with gastrointestinal stromal tumors: the ADAGIO study. *Anticancer Research, 31,* 1407-1410.

Malbasa, T., Kodish, E., & Santacroce, S. J. (2007). Adolescent adherence to oral therapy for leukemia: A focus group study. *Journal of Pediatric Oncology Nursing, 24,* 139-151.

Marin, D., Bazeos, A., Mahon, F. –X., Eliasson, L., Milojkovic, D., Bua, M., …Khorashad, J. S. (2010). Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *Journal of Clinical Oncology, 28*(14), 2381-2388. doi: 10.1200/JCO.2009.26.3087

Massarelli, E., Varella-Garcia, M., Tang, X., Xavier, A. C., Ozburn, N. C., Liu, D. B., …Wistuba, I. I. (2007). KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *Clinical Cancer Research, 13,* 2890 –2896. doi: 10.1158/1078-0432.CCR-06-3043

McCoy, L. (2009). Time, self and the medication day: A closer look at the everyday work of 'adherence.' *Sociology of Health and Illness, 31*(1), 128-146. doi: 10.111/j.1467-9566.2008.01120.x

Miles, M. B. & Huberman, A. M. (1994). *Qualitative data analysis: An expanded sourcebook* (*2nd ed*). Sage: Thousand Oaks, CA.

Miller, V. A., Riley, G. J., Zakowski, M. F., Li, A. R., Patel, J. D., Heelan, R. T., …Johnson, D.H. (2008). Molecular characteristics of bronchoalveolar carcinoma and adenocarcinomas, bronchoalveolar subtypes predict response to erlotinib. *Journal of Clinical Oncology, 26,* 1472-1478. doi: 10.1200/JCO.2007.13.0862

Molina, J. R., Yang, P., Cassivi, S. D., Schild, S. E., & Adjei, A. A. (2008). Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. *Mayo Clinic Proceedings, 83*(5), 584-594.

National Comprehensive Cancer Network (NCCN). (2011). Practice guidelines in oncologyTM: Non-small cell lung cancer. V3.2011. Retrieved April 4, 2011 from http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

National Cancer Institute (NCI) (2011). Costs of cancer care. Retrieved April 4, 2011 from: http://progressreport.cancer.gov/doc_detail.asp?pid=1&did=2007&chid=75&coid=726&mid.

National Cancer Institute (NCI) Fact Sheet for Targeted Therapy. Retrieved May 23, 2008 from: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted.

Neal, J. W. (2010). Histology matters: Individualizing treatment in non-small cell lung cancer. *The Oncologist, 15*, 3-5. doi: 10.1634/theoncologist.2009-0306.

Noens, L., Lierde, M. –A., De Bock, R., Verhoef, G., Zachee, P., Bernamen, Z., …Abraham, I. (2009). Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study. *Blood, 113*, 5401-5411. doi: 10.1182/blood-2008-12-196543

Oakley, C., Johnson, J., & Ream, E. (2010). Developing an intervention for cancer patients prescribed oral chemotherapy: a generic patient diary. *European Journal of Cancer Care, 19*, 21-28.

Orr, A., Orr, D., Willis, S., Holmes, M., & Britton, P. (2007). Patient perceptions of factors influencing adherence to medication following kidney transplant. *Psychology, Health & Medicine, 12*(4), 509-517.

Osterberg, L. & Blaschke, T. (2005). Adherence to medication. *The New England Journal of Medicine, 353*, 487-497.

Partridge, A. H., Wang, P. S., Winer, E. P., & Avorn. J. (2003). Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *Journal of Clinical Oncology, 21*(4), 602-606. doi: 10.1200/JCO.2003.07.071

Partridge, A. H., LaFountain, A., Mayer, E., Taylor, B. S., Winer, E., & Snis-Alibozek, A. (2008). Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *Journal of Clinical Oncology, 26*(4), 556-562. doi: 10.1200/JCO.2007.11.5451

Patton, M. Q. (2002). *Qualitative Research & Evaluation Methods* (3rd ed). Thousand Oaks, CA: Sage Publications, Inc.

Perez-Soler, R., Delord, J. P., Halpern, A., Kelly, K., Krueger, J., Sureda, B. M, …Leyden, J. (2005). HER1/EGFR Inhibitor-associated rash: Future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *The Oncologist, 10*, 345-356. doi: 10.1639/theoncologist.10-5-345

Perez-Soler, R. & Saltz, L. (2005). Cutaneous adverse effects with HER1/EGFR-targeted agents: Is there a silver lining? *Journal of Clinical Oncology, 23*, 5235-5246.

Piette, J., Heisler, M., & Wagner, T. (2004). Cost-related medication underuse among chronically ill adults: the treatments people forgo, how often, and who is at risk. *American Journal of Public Health, 94*(10), 1782-1787.

Press, M. & Lenz, H. -J. (2007). EGFR, HER2, and VEGF pathways. *Drugs, 67*(14), 2045-2075.

Proulx, M., Leduc, N., Vanderlac, L., Gegoire, J. -P., & Collin, J. (2007). Social context, the struggle with uncertainty, and subjective risk as meaning-rich constructs for explaining HBP noncompliance. *Patient Education and Counseling, 68*, 98-106. doi:10.1016/j.pec.2007.05.014

Reid, M., Clark, A., Murdoch, D. L., Morrison, C., Capewell, S., & McMurray, J. (2006). Patient strategies for managing medication for chronic heart failure. *International Journal of Cardiology, 109*, 66-73. doi:10.1016/j.ijcard.2005.05.051

Remien, R. H., Hirky, A. E., Johnson, M. O., Weinhardt, L. S., Whittier, D., & Le, G. M. (2003). Adherence to medication treatment: A qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities. *AIDS and Behavior, 7*(1), 61-72. doi: 10.1023/A:1022513507669.

Rifkin, D. E., Laws, M. B., Rao, M., Balakrishnan, V. S., Sarnak, M. J., & Wilson, I. B. (2010). Medication adherence behavior and priorities among older adults with CKD: A semistructured interview study. *American Journal of Kidney Disease, 5*(3), 39-46. doi: 10.1053/j.ajkd.2010.04.021

Rolley, J. X., Davidson, P. M., Dennison, C. R., Ong, A., Everett, B., & Salamonson, Y. (2008). Medication adherence self-report Instruments: Implications for practice and research. *Journal of Cardiovascular Nursing, 23*(6), 497-505.

Rosenblum, R., Deeks, S. G., van der Laan, M., & Bangsberg, D. R. (2009). The risk of virologic failure decreases with duration of HIV suppression, at greater than 50% adherence to antiretroviral therapy. *PLoS ONE, 4*(9), e7196.

Ruppar, T. M., & Russell, C. L. (2009). Medication adherence in successful kidney transplant recipients. *Progress in Transplantation, 19*(2), 167-172.

Russell, C. L., Kilburn, E., Conn, V. S., & Ashbaugh, C. (2003). Medication-taking beliefs of adult renal transplant recipients. *Clinical Nurse Specialist, 17*(4), 200-208.

Sandelowski, M. (1985). Sample size in qualitative research. *Research in Nursing and Health, 18*, 179-183.

Sandelowski, M. (1986). The problem of rigor in qualitative research. *Advances in Nursing Science*, 27-37.

Sandelowski, M., Holditch-Davis, D., & Glenn Harris, B. (1989). Artful design: Writing the proposal for research in the naturalist paradigm. *Research in Nursing and Health, 12*, 77-84.

Sandler, A., Gray R., Perry, M. C., Brahmer, J., Schiller, J. H., Dowlati, A., …Johnson, D. H. (2006). Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *New England Journal of Medicine, 355,* 2542-2550.

Sandler, A. B. (2008). NSCLC targeted therapy clinical research update. Presented at *Targeted Therapies for Non-Small Cell Lung Cancer: Expert Responses to Frequently Asked Questions* on May 14, 2008 as part of the Educational Symposium during the ONS 33rd Annual Congress, Philadelphia, PA.

Schatzman, L. (1991). *Dimensional analysis: Notes on an alternate approach to the grounding of theory in qualitative research*. New York, NY: Aldine de Gruyter.

Schindler, T., Bornmann,. W., Pellicena P., Miller, W. T., Clarkson, B., & Kuriyan, J. (2000). Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. *Science, 289,* 1938-1942.

Sedjo, R. L. & Devine, D. (2011). Predictors of non-adherence to aromatase inhibitor therapy among commercially insured women with breast cancer. *Breast Cancer Research and Treatment, 125,* 191-200. doi: 10.1007s10549-010-0957-6

Segaert, S. & Van Cutsem, E. (2005). Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Annals of Oncology, 16,* 1425-1433.

Sequist, L. V., Martins, R. G., Spigel, D., Grunberg, S. M., Spira, A., Janne, P. A., …Lynch, T. J. (2008). Gefitinib in patients with advanced non-small cell lung cancer harboring somatic EGFR mutations. *Journal of Clinical Oncology, 26,* 2442-2449. doi: 10.1200/JCO.2007.14.8494

Siegel, R., Naishadham, D., & Jemal, A. (2012). Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians, 62*(10), 10-29. doi: 10.3322/caac.20138

Sipples, R. (2006). Common side effects of anti-EGFR therapy: acneiform rash. *Seminars in Oncology Nursing, 22*, 28. doi: 10.1016/j.soncon.2006.01.013

Slebos, R. J., Kibbelaar, R. E., Dalesio, D., Kooistra, A., Stam, J., Meijer, A. L. M., …Rodenhuis, S. (1990). K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *New England Journal of Medicine, 323*, 561-565.

Spiers, M. V. & Kutzik, D. M. (1995). Self-reported memory of medication use by the elderly. *American Journal of Health-System Pharmacists, 52*, 985-990.

Spreen, O. & Strauss, E. (1998). *A Compendium of Neuropsychogical Test: Administration, Norms, and Commentary*. New York: Oxford University.

St. Charles, M., Bollu, V. K., Hornyak, E., Coombs, J., Blanchette, C. M., & DeAngelo, D. J. (2009). Predictors of treatment non-adherence in patients treated with imatinib mesylate

for chronic myeloid leukemia (Abstract 2209). Poster presented at the *51st ASH Annual Meeting and Exposition*, New Orleans, LA.

Szetela, A. B. & Gibson, D. E. (2007). How the new oral antineoplastics affect nursing practice. *American Journal of Nursing, 107*(12), 40-48.

Talpaz, M., Silver, R. T, Druker, B. J, Goldman, J. M., Gambacorti-Passerini, C., Guilhot, F., …Sawyers, C. L. (2002). Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood, 99,* 1928-1937.

Securities Exchanges Commission. (2008). Tarceva® Pricing Information. OSI Pharmaceuticals, Inc. Retrieved July 1, 2008 from: http://www.secinfo.com/dsvr4.z5wv.b.htm.

Tarceva® Package Insert. (2010). Melville, NY: OSI Pharmaceuticals, Inc. Retrieved May 4, 2011 from: http://www.gene.com/gene/products/information/pdf/tarceva-prescribing.pdf.

Taxol® Package Insert. (2008). Retrieved June 23, 2008 from: http://packageinserts.bms.com/pi/pi_taxol.pdf.

Thompson, A. M., Johnson, A., Quinlan, P., Hillman, G., Fontecha, M., Bray, S. E., …Newman, W. G. (2011). Comprehensive CYP2D6 genotype and adherence affect outcome in breast cancer patients treated with tamoxifen monotherapy. *Breast Cancer Research and Treatment*, 125, 279–287. doi: 10.1007/s10549-010-1139-x

Tilley, C. (2001). Ethnography and material culture. In, Atkinson, P., Coffey, A., Delamont, S., Lofland, J., & Lofland, L., Eds., *Handbook of Ethnography*. London: Sage.

Timmers, L., Boons, C. L. M. C., Mangus, D., Moes, J. E., Swart, E. L., Boven, E., …Hugtenburg, J. G. (2011). The use of erlotinib in daily practice: a study on adherence and patients' experiences. *BMC Cancer, 11*, 284. doi: 10.1186/1471-2407-11-284

U.S. Census Bureau. (2012). American fact finder. Accessed on July 20, 2012 at: http://factfinder2.census.gov/faces/nav/jsf/pages/searchresults.xhtml?refresh=t.

U.S. Census Bureau. (2012). State and county quick facts. Accessed on July 20, 2012 at: http://quickfacts.census.gov/qfd/states/42/4261000.html.

Veehof, L. J. G., Stewart, R. E., Haaijer-Ruskamp, F. M, & Meyborn-de Jong, B. (2000). The development of polypharmacy: A longitudinal study. *Family Practice, 17*, 261-267. doi: 10.1093/fampra/17.3.261

Viele, C. (2007). Managing oral chemotherapy: The healthcare practitioner's role. *American Journal of Health-System Pharmacists, 64*(Supp 5), S25-S32. doi: 10.2146/ajhp070037

Vik, S. A., Hogan, D. B., & Patten, S. B. (2006). Medication nonadherence older adults. *Drugs & Aging, 3*, 345-356.

Waterhouse, D. M., Caizone, K. A., Mele, C., & Brenner, D. E. (1993). Adherence to oral tamoxifen: A comparison of patient self-report, pill counts, and microelectronic monitoring. *Journal of Clinical Oncology, 11*(6), 1189-1197.

World Health Organization (WHO). (2003). Adherence to long-term therapies: Evidence for action. Geneva, Switzerland.

Wickersham, K., Happ, M. B., & Bender, C. M. (under review). "Keeping the boogie man away": Medication self-management among women receiving anastrozole therapy. Submitted to *Nursing Research and Practice* on June 11, 2012.

Wickersham, K., Happ, M. B., & Bender, C. M. (2011). Self-reported side effects and side effect severity regarding medication-taking for women with breast cancer taking oral aromatase inhibitor therapy [Abstract BU]. *Oncology Nursing Forum, 38*(1), A1-A90. doi: 10.1188/11.ONF.E60

Wickersham, K., Happ, M. B., & Bender, C. M. (September 2010). Medication-taking for hormonal therapy in breast cancer [Abstract]. National State of the Science Congress for Nursing Research of the Council for the Advancement of Nursing Science Book of Proceedings.

Winkeljohn, D. (2007). Oral chemotherapy medications: The need for a nurse's touch. *Clinical Journal of Oncology Nursing, 11*(6), 793-796.

Xeloda® Prescribing Information. (2012). Genentech. Accessed on June 14, 2012 at: http://www.gene.com/gene/products/information/xeloda/pdf/pi.pdf.

Ziller, V., Kalder, M., Albert, U. -S., Holzhauer, W., Ziller, M., Wagner, U., & Hadji, P. (2009). Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Annals of Oncology, 20,* 431-436. doi: 10.1093/annonc/mdn646